Section of Medicine

President E R Cullinan MD

Meeting October 25 1960

Diuretics

The Physiological Basis of Diuretic Action

by A A G Lewis MD (*London*)

Considering the sodium flux through the kidneys of a subject in sodium balance on an ordinary sodium intake of 100 mEq in twenty-four hours, we find that nearly the whole of that amount of sodium passes through the kidneys *every minute*, but that only about 0·25 mEq escapes in the urine. Within the kidney about 18 mEq are filtered through the glomeruli every minute, of which nearly 15 are reabsorbed in the proximal tubule. In the loop of Henle about 1 mEq is reabsorbed in the counter-current system that produces the hypertonic medullary zone necessary for the formation of a concentrated urine. In the distal tubule a similar quantity is reabsorbed by the ion-exchange mechanism which replaces sodium ions in the tubular lumen by potassium or hydrogen ions, partly under the influence of aldosterone and glucocorticoids.

Glomerular filtration is normally adjusted to renal plasma flow so that approximately one-fifth of the flow is filtered off; if the blood flow falls this filtration fraction rises so that the glomerular filtration rate (G.F.R.) is partly maintained. In many patients who are forming œdema, however, the G.F.R. falls sufficiently to reduce the filtered sodium by an amount many times greater than the fraction of 1 mEq previously being excreted, so that if tubular reabsorption were maintained at its previous level no sodium would be excreted at all. This cannot be the only cause of sodium retention, however, for œdema can form when the G.F.R. is normal or above normal, and moderate reduction of G.F.R. in normal man does not greatly reduce sodium retention (Chalmers *et al.*, 1952).

In the distal tubule aldosterone stimulates the reabsorption of sodium, partly in exchange for potassium and hydrogen ions. The latter are made available in tubular cells by the ionization of carbonic acid, formed from the combination of carbon dioxide and water under the influence of carbonic anhydrase within the cells. The factors controlling the rate of secretion of aldosterone in the adrenal cortex are still not fully understood, but there is no doubt that one of them is a change in extracellular fluid (E.C.F.) volume. When a normal person increases his sodium intake this volume is increased and aldosterone secretion suppressed. Obviously this homeostatic mechanism must be deranged in some way in œdematous states, for both the rate of secretion of the hormone and the E.C.F. volume may be increased simultaneously. Yet this cannot be the sole cause of œdema formation, for œdema is not a feature of hyperaldosteronism, while adrenalectomized dogs with experimental valvular lesions may retain sodium when given aldosterone in amounts less than those needed to maintain sodium balance in dogs with no adrenals but with normal hearts (Davis 1960).

It is important to remember that the secretion of one other hormone, namely antidiuretic hormone (ADH), is partly controlled by a volume mechanism. Normally, ADH adjusts renal water loss so that changes in sodium balance do not lead to changes in the tonicity of E.C.F., but the normal collaboration between the salt-retaining and water-retaining hormones may occasionally be broken in œdematous patients, with a dilution of body fluids.

The accumulation of œdema, therefore, cannot always be explained by either a glomerular or a tubular mechanism: each of these factors has had its supporters but most people take refuge in the useful phrase 'glomerulotubular imbalance' and so get it both ways. The fact is that many of the circulatory factors that tend to lower the G.F.R., such as hypovolæmia and a low cardiac output, tend also to stimulate tubular reabsorption of sodium and water by the volume-regulating mechanism.

Diuretics produce their effect by modifying one or more of these processes of filtration and reabsorption. Digitalis, by increasing the cardiac output, increases renal blood flow and G.F.R., but it has a direct, though less important, effect on renal tubular sodium reabsorption as well (Farber *et al.* 1951). The xanthine diuretics also have multiple actions, the most useful being to increase the renal blood flow. Osmotic diuretics, such as urea and mannitol, oppose the reabsorption of water in the proximal tubule and so reduce the concentration of sodium in its lumen, thereby limiting its reabsorption at this site. Increased amounts of filtrate are therefore carried on to the distal tubules, whose relative effectiveness is thereby reduced. Two factors limit the effectiveness of osmotic diuretics by themselves in severely ill patients – the low G.F.R. limits the quantity delivered to the tubules while a greatly increased secretion of aldosterone may lead to distal reabsorption of most of the extra sodium leaving the proximal tubules.

Mercurials block the proximal tubular reabsorption of sodium. They are known to reduce the number of available protein-bound sulphhydryl groups, an action reversed by B.A.L. which also antagonizes their diuretic activity, so that it is reasonable to assume a connexion between these effects. Levy *et al.* (1958) believe that rupture of the carbon-mercury bond in acid solution, with liberation of mercuric ions, is necessary for the diuretic action to occur, the divalent mercuric ion inactivating both a sulphhydryl group and a second group in the tubular enzyme system. Farah & Kruse (1960) have shown that the number of protein-bound sulphhydryl groups in the cells of the terminal part of the proximal tubules, of Henle's loop and of the collecting ducts are reduced by mersalyl. B.A.L. reverses this change; acidosis increases and alkalosis reduces both this change and the diuretic effect of the drug. These effects of acid-base changes are compatible with the hypothesis of Levy *et al.*, for all the diuretic mercurials are acid-labile. Orloff (1961) has shown that ammonium salts all potentiate mercurial diuresis, presumably by producing an intracellular acidosis. The only facts difficult to fit in with this hypothesis are the failure of respiratory acidosis and of acetazolamide, both of which produce intracellular acidosis, to potentiate the action of mercurials.

Mercurials not only increase the excretion of sodium and chloride: they increase the free water clearance and reduce the concentration of the urine in hydropenic subjects to a greater degree than osmotic diuretics do. Au & Raisz (1960) suggest that this may be because they inhibit sodium transport in the loop of Henle (a site where they have been shown to affect sulphhydryl groups) and so interfere with the concentrating mechanism.

Salts such as ammonium chloride are diuretic, since they impose a chloride load upon the kidney excreted with sodium in the first instance. Given with mercurials, however, ammonium chloride also tends to maintain the plasma chloride level and to potentiate the action of the mercurial by its acidifying action.

Inhibitors of carbonic anhydrase, such as acetazolamide, reduce the availability of hydrogen ions in the distal tubular exchange for sodium, so that less sodium is reabsorbed and less hydrogen excreted; potassium ions from the interior of the cell are exchanged instead of hydrogen ions for sodium so that the urine becomes alkaline, and contains an increased amount of potassium and bicarbonate. The benzothiadiazine group of drugs, of which chlorothiazide was the first to be discovered and bendrofluazide is the latest, act on both proximal and distal tubules.

Aldosterone may play a double role in patients with œdema: it may not only contribute to the œdema, but may greatly limit the effectiveness of therapy and bring about potassium depletion. The production of drugs which either suppress the secretion of this hormone or interfere with its effects on tubular cells is therefore of great practical importance. Amphenone, which suppresses its secretion, is too toxic for clinical use, though other similar agents are becoming available. Both progesterone and adrenal glucocorticoids may modify to some extent the tubular action of aldosterone (Landau & Lugibihl 1958; Uete & Venning 1960) and this may be one cause of the diuretic effect of steroids in severely ill patients with œdema (Heidorn & Schemm 1955). A contributory effect is probably the increase of G.F.R. produced by glucocorticoids.

Recently a group of compounds, the spirolactones, has been produced which effectively antagonize the action of aldosterone at the renal tubular level.

Resistance to diuretics may occur for a number of different reasons. A low G.F.R. reduces their effectiveness, since less filtrate is delivered to the site of action, and hyponatræmia has a similar effect. Mercurials tend to be inhibited by metabolic alkalosis and hypochloræmia, both of which are corrected by ammonium chloride. An intravenous injection of aminophylline may restore the response to mercury by increasing the

G.F.R. More recently it has been shown that an infusion of a hypertonic solution of l-arginine hydrochloride may restore mercury responsiveness (Gidekel *et al.* 1960). The reason is obscure, since neither the acidosis nor the increase in plasma chloride produced is great. This may prove a valuable measure in hepatic cirrhosis where ammonium chloride should not be given. The action of acetazolamide is soon limited by the metabolic acidosis which it produces.

The localization of the sites of action of various diuretic agents, partly made possible by the stop-flow technique, has made the intelligent use of combinations of diuretics possible. It seems probable that a great deal of the sodium reabsorption that occurs when the G.F.R. is low takes place high up in the proximal tubule. Increasing the G.F.R. by intravenous aminophylline, or increasing proximal tubular flow by infusing mannitol, will bring more filtrate to the site of action of mercurials or chlorothiazide, whose effects will be enhanced. Moreover, since these agents affect different transport systems, their actions too may be synergistic when given together. The effect of a much greater load of sodium arriving distally at the site for ion-exchange may then result in a greatly increased output of potassium, when the addition of a spirolactone may be effective, countering the action of aldosterone at this site. These examples indicate the value of biochemistry in helping the treatment of resistant cases. It is not necessary to be able to estimate the urinary aldosterone in order to treat congestive failure effectively. But an interested physician, who studies not only the changes in plasma electrolyte levels but collects urine passed by patients who have received diuretics with an unsatisfactory response to discover the reason for this, will get very much better results in the long run than one who does not.

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The Renal Action of Chlorothiazide

by A G Spencer GM MRCP (*London*)

In many aspects of medicine discussion expands to fill the space made available by lack of data. Such is not the position with diuretics. During the past five years some twenty new diuretics have been introduced and more than two thousand papers have been published describing their use. Some of these represent a distinct advance in our therapeutic knowledge, while others merely extol the allegedly superior virtues of the latest drug. As with other potent drugs the thiazides may produce undesirable and occasionally disastrous side-effects, and it is the mechanism of these complications which I shall discuss. Benzothiazide diuretics work mainly by inhibiting those enzyme systems in the renal tubules which are concerned with the transport of ions. Glomerular filtration is also reduced. This is an example of the common therapeutic paradox of a drug which improves the patient's condition by making him worse, in the sense that a highly specialized physiological process is deliberately impaired by an even more specific pharmacological action.

The formation of the glomerular filtrate is dependent on energy supplied by the contraction of the heart and transferred to the kidney by the blood stream. This is the purpose of the normal high renal blood flow of some 1,200 ml/min. Thiazide diuretics reduce the glomerular filtration rate (G.F.R.). This would result in a profound antidiuresis were it not for the action of thiazides on the renal tubules.

The intravenous administration of chlorothiazide in the dog usually results in a 20% reduction of the inulin clearance or G.F.R., with little change in the C_{PAH} or the estimated renal plasma flow (Table 1). Notice that the clearance of chlorothiazide greatly exceeds the filtration rate, indicating the tubular secretion of this drug.

Table 1

Effect of chlorothiazide on the inulin and PAH clearances in the dog

	Clearances ml/min		
Period	*PAH*	*Inulin*	*Chlorothiazide*
Control (i)	212	48	—
Control (ii)	218	46	—
Chlorothiazide (i)	204	39	127
Chlorothiazide (ii)	198	37	118

Intravenous chlorothiazide (500 mg) produces a similar fall in the G.F.R. in man (Fig 1). This occurs before there is any considerable loss of water and electrolytes in the urine, and it is not due to a reduction in plasma volume. There is

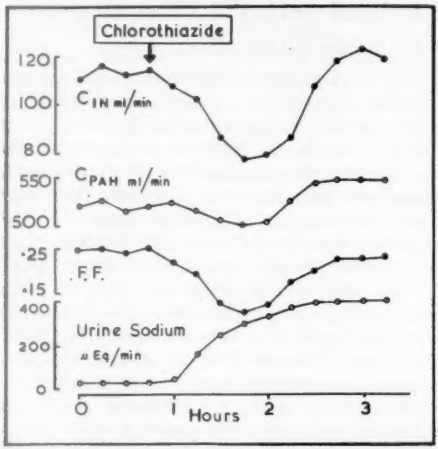

Fig 1 *Effect of intravenous chlorothiazide on renal clearances in man*

only a small fall in the renal blood flow. In this hypertensive patient there was a marked reduction in the filtration fraction (F.F.) from 0·26 to 0·15. This represents a decrease in the renal vascular resistance, the cause of which is unknown. It may be due to a direct action of the drug on the renal arterioles, to a decrease in the sodium content of the muscle in the renal vessels, or possibly to a reduction in the interstitial pressure of the kidney consequent on a loss of sodium from the tubular cells. It is probably a local expression of a general action of thiazides on small blood vessels, since it has recently been shown that chlorothiazides reduce the total peripheral vascular resistance.

It is important for the physician to be aware of the fall in the G.F.R. which may be produced by this group of diuretics. While in many patients this action is small and of no consequence, in others it may be relatively large, especially in subjects whose renal function is already impaired by disease. Substances which are mainly excreted by glomerular filtration – i.e. those for which tubular secretion is unimportant – may then accumulate in the body, for example urea, uric acid, antibiotics such as streptomycin, and many drugs.

In one hypertensive patient (Fig 2) the administration of 1 g of chlorothiazide a day for seven days resulted in a fall in the G.F.R. from 40 to 22 ml/min and the blood urea rose from 90 to over 200 mg/100 ml. There was a fall in the blood pressure and in the plasma volume as measured with ^{131}I-iodinated albumin. This upset was reversed by withdrawing the drug and giving extra salt. Cocoran *et al.* (1959) have reported a similar experience. The effects of prolonged treatment with chlorothiazide resemble those produced by the rice diet. Healey *et al.* (1959) have found that benzothiazide diuretics reduce the excretion of urates. There is an elevation in the serum uric acid, and an acute attack of gout may occur. This is a complex action, partly due to the lowered G.F.R. and filtered load of urates and in part due to a reduction in the renal tubular secretion of this ion.

There is one group of patients in whom this fall in G.F.R. may be of therapeutic benefit, those with nephrogenic diabetes insipidus. In diabetes insipidus prolonged administration of thiazide diuretics results in a 50% reduction of the daily volume of urine. The mechanism of this antidiuresis is disputed (Crawford *et al.* 1960). Havard and Wood (1960) have demonstrated that it is accompanied by a 30–50% fall in the G.F.R. Both the antidiuretic action and the decrease in G.F.R. are reversed by giving salt.

Tubular transport: The action of the thiazide drugs on the renal tubules may be investigated by clearance studies, by experiments on metabolizing kidney slices and by stop-flow analysis. These have been fully described and illustrated in the *Proceedings* (Spencer 1960) and elsewhere (Spencer 1959).

The inhibition of the tubular reabsorption of sodium chloride results in an osmotic diuresis and consequent relief of œdema. The increased loss of potassium in the urine produced by thiazide diuretics may produce hypokalæmia and extracellular alkalosis. This is particularly unfortunate since these drugs are most widely used in patients who already have a potassium deficiency state, namely in heart failure, hepatic cirrhosis, the nephrotic syndromes, severe hypertension, small intestinal disease and steroid-induced

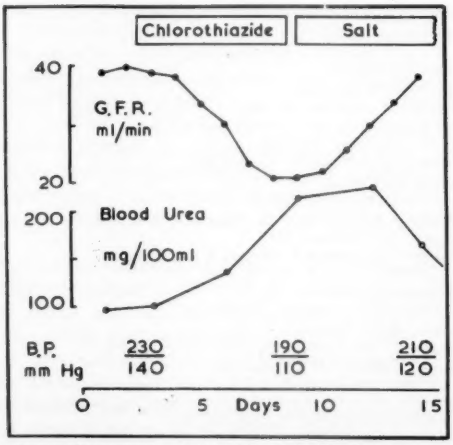

Fig 2 *Fall in G.F.R. during chlorothiazide therapy*

œdema. There is little convincing evidence that the more recently introduced thiazides, hydroflumethiazide (Blagg 1959, Edmonds & Wilson 1959) and bendrofluazide (Kennedy *et al.* 1960) and the allied drug chlorothiazide (Hygroton) cause a smaller loss of potassium in the urine.

The main hazards of potassium deficiency are sensitization to digitalis, hepatic coma, muscular weakness and paralysis and hypokalæmic nephropathy. An effective remedy is to give potassium chloride 1 g t.d.s. during thiazide treatment. An alternative is the combined use of thiazides and aldosterone antagonists.

A further serious hazard of thiazide treatment results from the inhibition of distal tubular hydrogen ion secretion. A rise in urine pH decreases the rate of excretion by non-ionic diffusion of weak organic bases such as mecamylamine and pempidine. The accumulation of hypotensive drugs may produce an excessive fall in blood pressure, a further reduction in G.F.R. and renal failure. Combined therapy with chlorothiazide, a ganglion blocker and digitalis is not rarely fatal. Since the uræmic patient cannot excrete these drugs the condition is self-perpetuating. In our experience treatment by hæmodialysis has been successful; it simultaneously removes the drugs, corrects the uræmia and the hypokalæmia.

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The Clinical Application of Aldosterone Antagonists in the Treatment of Œdema

by Stanley Shaldon MB MRCP (*London*)

The synthesis of the steroidal-17-spirolactone compounds with marked aldosterone antagonist properties (Cella & Kagawa 1957, Liddle 1958, Slater *et al.* 1959) has provided the most potent diuretic for the treatment of œdematous states associated with secondary hyperaldosteronism. Cirrhotic patients with fluid retention secrete more aldosterone than œdematous patients with other diseases (Ulick 1959). This communication deals with the use of the oral aldosterone antagonist, spironolactone (Aldactone, SC9420) in the treatment of patients with cirrhosis and ascites.

Clinical trials with an earlier intramuscular spirolactone, SC8109 (Kerr *et al.* 1958) were disappointing. Schedl & Bartter (1958) suggested that there was excessive proximal tubular reabsorption of sodium in cirrhotic patients with ascites and it was subsequently postulated that this mechanism was responsible for the failure of aldosterone antagonists to promote a sodium diuresis if used alone. It was suggested also that the combination of spironolactone with a proximal tubular diuretic of the thiazide series might produce a synergistic effect with a satisfactory sodium diuresis (Shaldon *et al.* 1960) (Fig 1). Evidence in support of this hypothesis was obtained by studying the effect of chlorothiazide and spironolactone, given alone and in combination, to 9 patients with cirrhosis and resistant ascites (Fig 2). All patients were resistant to chlorothiazide given alone, 2 patients experienced a small sodium diuresis and weight loss with spironolactone alone, but all patients showed a weight-losing sodium diuresis when the two diuretics were combined.

However, not all patients with cirrhosis and fluid retention require combined diuretic therapy. In the past eighteen months, since sufficient spironolactone has been available for clinical trial, 51 patients with cirrhosis and fluid retention have required some form of diuretic therapy. This group does not include patients in whom fluid retention was a terminal manifestation of liver failure, or a transient state following a hæmorrhage or operation. The patients were all treated at first with thiazide or mercurial diuretics, potassium supplements and a low salt diet. 33 patients (65%) responded to this regime but 18 (35%) required spironolactone in addition. Only 4 patients (8%) failed to achieve a satisfactory diuresis, and these 4 patients subsequently died of liver failure. Thus, approximately two-thirds of patients with cirrhosis and ascites or peripheral œdema may be adequately controlled with thiazide or mercurial diuretics and potassium alone, but all patients require a rigidly salt-restricted diet. Diuretic therapy is secondary to salt restriction.

I have studied recently a patient who was said to be resistant to chlorothiazide and spironolactone, but she was receiving an unrestricted salt intake. When put on a fairly low sodium diet she lost 2 kg in weight and subsequently her ascites was completely eliminated with chlorothiazide and potassium. Occasionally a patient will show an initially dramatic response to thiazide but then reaccumulate fluid in spite of continued therapy (Fig 3). The occasional cirrhotic patient retains sodium so avidly that he is resistant to thiazides or mercurial diuretics from the onset of treatment. Under these circumstances spironolactone is indicated.

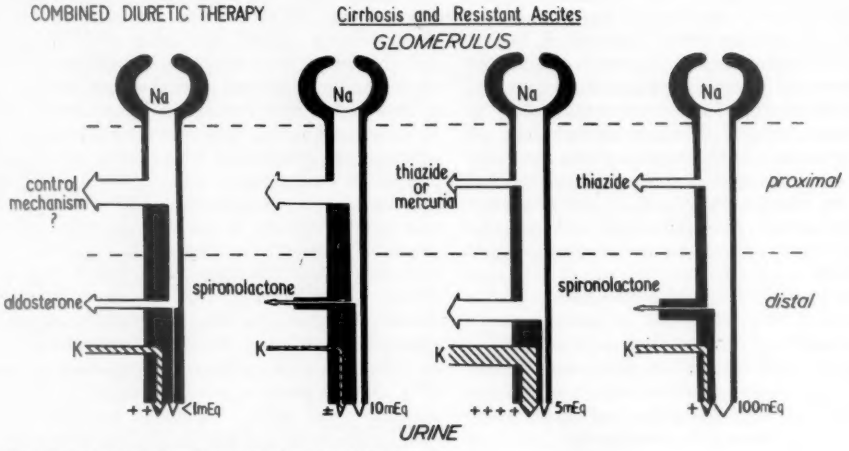

Fig 1 *Renal tubular handling of sodium in cirrhosis with resistant ascites. The majority of filtered sodium is reabsorbed proximally to the distal site of aldosterone action. Potassium is exchanged for sodium at this distal site. The urine contains less than 1 mEq of sodium per twenty-four hours and there is excess potassium loss. Spironolactone blocks distal tubular reabsorption of sodium but, as the majority of sodium is reabsorbed proximally, only a small sodium diuresis results; but the potassium loss is decreased. Thiazides or mercurial diuretics block proximal tubular reabsorption of sodium, sodium is reabsorbed distally under the influence of aldosterone; little sodium reaches the urine and potassium loss is excessive. Blockade of proximal and distal sites of sodium reabsorption with combined diuretic therapy result in a satisfactory clinical diuresis, but potassium loss may be increased*

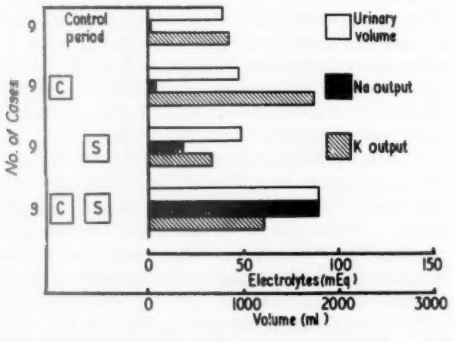

Fig 2 *Mean twenty-four-hour urinary volume, and sodium and potassium output in patients with cirrhosis and resistant ascites during treatment with spironolactone (S) 400 mg daily for three days; and chlorothiazide (C) 2 g daily for three days, alone and in combination. The means for each patient were derived from a five-day collection starting with each three-day course*

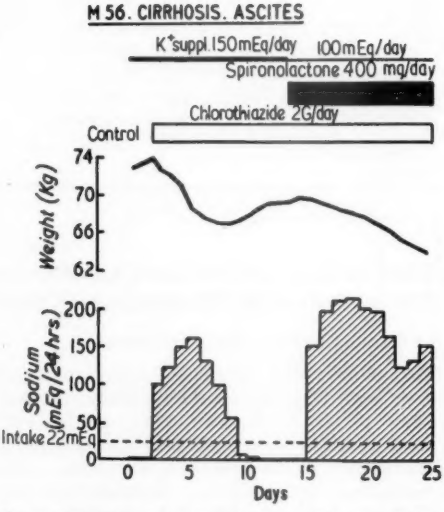

Fig 3 *Indication for spironolactone therapy. Patient with cirrhosis and ascites initially responded to chlorothiazide then became resistant. On the addition of spironolactone the ascites was satisfactorily controlled*

Recommended Diuretic Regimen for Patients with Cirrhosis

(1) Rigid salt restriction (22 mEq Na) and bed rest.

(2) Chlorothiazide 2 g daily (or equivalent dose of any thiazide) with potassium supplements (100–150 mEq daily) given as an effervescent tablet containing 6·5 mEq of potassium (potassium bicarbonate 500 mg and potassium acid tartrate 300 mg). These potassium tablets were devised by the Pharmacy Department of the Royal Free Hospital (Hadgraft 1960). If the patient has a history of hepatic precoma or shows overt signs of chronic portal systemic encephalopathy (Sherlock *et al.* 1954), mersalyl 2 c.c I.M. on alternate days is preferable to thiazide therapy.

(3) If thiazide therapy has not produced a satisfactory diuresis within one week (weight loss of 1–2 kg), spironolactone should be added in an initial dosage of 400 mg per day, and potassium supplements continued at a reduced rate of 50–100 mEq per day. A satisfactory diuresis will usually begin within two or three days and the patient will lose about 0·2–0·5 kg per day. The diuresis is slow and steady and the patient often requires twelve weeks of uninterrupted combined diuretic therapy in hospital to eliminate the ascites completely.

(4) Occasionally a patient will be resistant to this combination and if after one week on combined therapy a satisfactory diuresis has not begun, spironolactone should be increased to 600–1,000 mg per day. The reason for this is that the absorption of spironolactone is variable and some patients appear resistant on 400 mg per day as they are absorbing less of the drug.

(5) If the patient is still resistant after increasing the dosage of spironolactone, then an osmotic diuretic (e.g. mannitol 10% 2 l. I.V. over eight hours given on alternate days for one week) may initiate a diuresis. Alternatively, prednisone 10 mg q.d.s. may be tried, although the dangers of sepsis associated with steroid therapy in patients with ascites makes this choice less preferable.

(6) *Maintenance diuretic therapy:* Patients with cirrhosis will usually require diuretic therapy and salt restriction to prevent reaccumulation of fluid on discharge from hospital. Maintenance doses of chlorothiazide when used alone are best given as 2 g on alternate days with daily potassium supplements. Only three patients who required spironolactone initially were able to maintain themselves free of fluid on thiazides alone. The remaining fifteen patients are receiving spironolactone and chlorothiazide on five days out of seven, and potassium supplements daily. Several of these patients have now had spironolactone for over one year without obvious side-effects. The long-term benefit of combined diuretic therapy is not necessarily seen in the immediate post-ascitic stage, but after several months, when evidence of reaccumulation of flesh and a marked improvement in general health may be observed.

Complications of Diuretic Therapy

Although the diuretic combinations are effective in treatment certain complications may occur and a careful watch must be kept for them. Any effective diuretic may send a patient with cirrhosis and ascites into hepatic coma by producing an electrolyte imbalance. Under such circumstances all diuretic therapy should be stopped and restarted very cautiously only after the coma has been treated (Sherlock *et al.* 1956). Thiazides are particularly dangerous in this respect (Read *et al.* 1958), and the potassium loss in the urine may produce symptoms of hypokalæmia, and the associated alkalosis may result in cramps or overt tetany. Giving potassium will usually prevent these complications, but the use of a thiazide diuretic alone in a patient with a history of hepatic precoma is best avoided. Under such circumstances mercurial diuretics are safer.

Patients on combined diuretic therapy tend to develop an asymptomatic hyponatræmia, which is probably due to sodium loss in excess of water; occasionally precoma or coma may ensue. Mannitol or water restriction will correct this hyponatræmia, or if the therapy is given for five days out of seven, then the hyponatræmia tends to correct itself.

Conclusion

Combined diuretic therapy has virtually eliminated the problem of resistant ascites but has added considerably to the difficulties in management of patients with ascites. Careful supervision and routine serum electrolyte determinations are essential; any symptoms or signs suggestive of hepatic precoma are an indication for stopping diuretic therapy. Some patients with cirrhosis prefer to be a little wet and wise, rather than dry and drowsy.

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Meeting November 22 1960

Discussion on Suicide

Characteristics of the Suicide-Prone

by Professor G M Carstairs MD FRCPED DPM
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One of the most remarkable facts about suicide, which has been pointed out by social historians for over a hundred years, is the regularity of its rate of occurrence in any particular population. This has stimulated many investigations into the sociological causes of high and low suicide rates. One of the earliest, and still one of the best, is that by Dürkheim (1897).

In preparing this paper I have drawn freely on two English monographs, on 'Suicide in London' (Sainsbury 1955) and 'Attempted Suicide' (Stengel & Cook 1958). Their titles are a reminder of the first distinction to be drawn in this field: those who commit suicide and those who survive after an attempted suicide are two distinct groups. Some writers have obscured the difference by pointing out that both groups have performed suicidal acts; Lindemann (1950) has gone further, describing suicide as 'the fatal case of a disease for which we have no name'. To remedy this he proposed the term 'hypereridism' for the morbid state of hostile tension which culminates in such an act. This is to suggest a homogeneity which the facts belie. Suicides, as a group, are clearly distinguishable from attempted suicides in several respects. They differ, for example, in their epidemiological characteristics. In one study there were twice as many cases of attempted as of successful suicide in the population surveyed. In those who attempted suicide there were more than twice as many women as men, but in the suicides the sex ratio was reversed. The suicides, unlike the others, were mainly over the age of 45 (Carstairs & Brown 1958).

Neither suicide nor attempted suicide is an illness; both are patterns of human behaviour, determined by a number of factors in which physical or mental illness, personality and environment each may play a part; and both have been the subject of systematic sociomedical research. Before referring to these inquiries in order to show some of the characteristics of the suicide-prone, one word of caution is needed: statistics tend to be incomplete because there are often strong social pressures to prevent accurate reporting of these events. For example, Southern Ireland has a reported suicide rate which is among the lowest in the world; but this is a country in which the Roman Catholic Church has great authority. It is doubtful whether there really are few suicides, or whether for religious reasons great pains are taken to represent suicide, when it occurs, as death from other causes. In England, on the other hand (though not in Scotland) attempted suicide is a criminal offence which can lead to a prison sentence. This undoubtedly gives rise to under-reporting of attempted suicide in official returns. As Epps (1957) has pointed out, objective study of these acts is not helped by society's pronouncement that those who succeed in suicidal attempts are of unsound mind, while those who fail are to be regarded as criminals.

With these reservations, we can nevertheless draw some guidance from past research. Studies both of suicide and of attempted suicide show that these acts are commonest among persons who are socially isolated. They occur with greater frequency in large cities than in country districts, but even in the metropolis suicide remains a relatively rare event. In any year there are about 12 suicides and perhaps 30 cases of attempted suicide per 100,000 population. This means that, in a general practice of 2,500, attempted suicide may be met a little less frequently than once a year, and suicide about once in three years; in country practices the rates will be lower.

It is clear therefore that large populations must be studied in order to show sociological correlations. Attention can then be directed to the dwellers in lodging-houses, hotel rooms and bed-sitting rooms, to members of immigrant minority groups, and to those who have lost their family ties. Single persons are more likely to commit suicide than the married, and for married men the risk diminishes progressively with each additional child – up to the number of 5 (Halbwachs 1930).

It is those people who lead isolated lives, deprived of contact either with family, friends, or a religious community, who are most exposed to the risk of suicide.

One high-risk group has attracted particular attention, namely the student population. The late Sir Alan Rook has summarized the facts:

Suicide comes second to accidents as a cause of death in students. Over a period of thirty-five years 103 undergraduate deaths were recorded in Cambridge; of these 41 were due to accident, 35 to suicide and 27 to disease. During the past decade the suicide rate among men students at Oxford and Cambridge has been three to five times higher than that for men of the same age in

England and Wales. At seven provincial universities the excess is much less marked and women students rarely commit suicide. In Cambridge, at least, there is evidence that the student suicide rate in the last decade was about the same as in the period 1928–38 (Rook 1959). As explanation Sir Alan Rook suggested that high academic standards may be associated with emotional instability in the student entry; and that college life demands a self-reliance which many students do not possess. The only suggested association supported by figures was the increased frequency of suicide during the period of examinations. Since, however, the early summer months are the peak period for suicides in the general public as well as in students, one cannot with confidence regard examination stress as a crucial factor.

It has to be remembered, especially now that the thymoleptic drugs are coming into general use, that the depressed patient passes through a period of increased suicidal risk during the early stages of his treatment. In some cases the retardation and loss of volition is relieved, while the mood remains at times quite depressed. Such patients regain power of initiative only to turn it against themselves. It has to be remembered that suicide is not always preceded by mental illness. Sometimes it is the result of a deliberate, considered choice as in individuals who are on the verge of exposure and disgrace, or who realize that they are suffering from a painful and incurable disease.

In a proportion of cases, the suicide gives warning of his intention: Robins and his collaborators (1959) found this to have been the case in 69% of 134 consecutive suicides. This is still more often found in cases of attempted suicide; indeed Stengel (Stengel 1952, Stengel & Cook 1958) has emphasized the 'appeal' character of this act.

Estimates have differed widely as to the frequency of psychiatric illness in attempted suicides. Dahlgren (1945) could not ascribe a psychiatric diagnosis in 58 out of 251 such cases, whereas Stengel & Cook (1958) ascribed a diagnosis to almost all of their large series. Robins & O'Neal (1958) found that none of 109 attempted suicides admitted to a general hospital was clinically well, although they could not fit a diagnosis to 18 of these patients. These, of course, are studies of hospitalized patients: many others are treated at home, and these may include a smaller proportion of the clinically ill. The Reverend Chad Varah, whose organization 'The Samaritans' now answers some 2,000 appeals a year from suicidal or despairing individuals, has said recently that 'The vast majority of them are not suffering from any mental illness' (Varah 1960). They are lonely and frustrated people, and often their loneliness and frustrations are aggravated by their own lifelong personality difficulties. The catalogue of characteristics of those who attempt suicide is unflattering: traits of dependency, egocentricity, sexual maladjustment, narcissism, inability to form friendships, of immaturity, and of hypersensitivity have all been described. These subjects have frequently been regarded as emotionally unstable and prone to sudden impulsive behaviour. Many of them have come to psychiatric attention before the attempt at suicide, and these are commonly diagnosed as showing hysterical or psychopathic personality.

There is often an aggressive element in the suicidal act, and this may be quite explicit, as in the suicide note quoted by Batchelor (1954*b*) which ran: 'Dear Dad, this is Good-bye. You haven't been much of a Dad to me – Johnny.' When the suicidal attempt becomes too obviously a threat, it mobilizes counter-aggression and its implicit appeal for help is less likely to be met. Public opinion, however, now increasingly recognizes that imprisonment is not the way to deal with these unfortunates. They need treatment, if necessary under compulsory orders. There are still all too many hospitals which neglect these patients' needs. At the very least, every case of attempted suicide should be seen by a psychiatrist and his future treatment planned before he is discharged from hospital.

As a result of social measures to control excessive drinking, alcoholism appears to have diminished in importance as a cause of suicide. Whereas in the last century alcoholics formed 77% of a group of attempted suicides studied in Liverpool (Sullivan 1898), the proportion of alcoholics in a similar series observed there forty years later had fallen by 13% (Hopkins 1937). Drinking to excess, especially when this is associated with manic-depressive illness or psychopathic personality, can certainly heighten the risk of an impulsive suicidal act (Glatt 1957, Batchelor 1954*a*).

It is important to consider whether people who have made one or more unsuccessful suicidal attempts should be regarded as especially suicide-prone. Stengel & Cook (1958) state that suicide is infrequent in persons who attempted suicide. Their own follow-up of 286 cases, which they admit is incomplete, revealed 6 (2·1%) subsequent suicides; Batchelor (1954*b*) found that 2% of 200 cases of attempted suicide had died by their own hand within one year. In other large series of attempted suicides followed up for several years subsequent suicide has been found in 6% (Dahlgren 1945), 4·8% (Hove 1953) and 9·1% (Schneider 1954). Even the smallest of these figures represents a suicide rate of 2,000 per

100,000 as compared with rates in the general population which do not usually exceed 20 per 100,000 per annum. It is abundantly clear that the warning of a suicidal gesture, and even of expressed suicidal intent, must never pass unheeded. This is particularly the case when it occurs in a person who may be suffering from depression and when the attempt has been a serious one. It is true to a lesser extent for patients who show hysterical, psychopathic or alcoholic symptoms and for previously stable persons who find themselves confronted with sudden, seemingly overwhelming, stress. These are the cases for which the physician must keep a vigilant watch.

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Dr Ian Stewart (Keighley) read a paper entitled **Suicide: The Influence of Organic Disease.** A full account of this paper will be found in the *Lancet*, 1960, ii, 919.

The Problem of Suicide in General Practice

by C A H Watts MD DRCOG (*Ibstock, Leicester*)

Suicide is essentially a disease of general practice. In Ibstock with some 8,000 patients at risk we have had 12 suicides in almost fifteen years. I know of no patient of ours during that time who committed suicide during a stay in hospital. It is very good to know that the Section of Medicine is interested in this subject because depression is no monopoly of the psychiatrist. We all have our quota of cases. We hear a great deal about the problem of death on the roads, and much useful propaganda is put out to try to lower those figures. The suicide problem is just as great and it deserves just as much attention. We all need to be much more aware of it, the public as well as the medical profession. It is one of the major problems of our age, and yet the depressive symptoms which so often precede the tragedy are overlooked or misinterpreted. This point may be illustrated by two striking case histories:

Case 1 A hospital porter began to get some peculiar ideas that the Russians were coming. His fellow porters pulled his leg about his queer talk, and they laughed as he dived under a table when he heard a plane passing overhead. They did not, however, laugh when they heard that he had killed his wife and children to save them from the Russians. He did not take his own life as he might well have done. I understand the man is still in Broadmoor having recovered after a course of E.C.T. 'Why in Heaven's name couldn't someone have helped me earlier?' he asks: and he, it will be noted, worked in a hospital.

Case 2 A general practitioner colleague of mine was confronted by a very anxious man who had organic symptoms. My friend decided to have a second opinion before passing the patient on to a psychiatrist. The consultant wrote: 'I examined your patient. I found no evidence of organic disease and I have thoroughly reassured him. I don't think you need worry about a psychiatrist.'

Before this letter had reached my colleague the man had hanged himself. The general practitioner, who knew the patient well, realized the man was anxious, but he missed the depression. The consultant, who had only a single interview with him, was even more at sea.

These two rather grim cases are described to show how we all miss or mismanage depressions, laity, general practitioners and consultants, and even psychiatrists!

In 2 of the 12 suicides in our practice the tragedy was completely unexpected. In 5 cases there was evidence of distress, but neither the patient nor the family had approached the doctor for help. In the other 5 cases the patient was known to be worried, depressed, or schizophrenic. 3 of these patients were under my personal care when they committed suicide. As a rough estimate I should say that in 8 of the 12 cases the tragedy was preventable; that is if on the one hand the relatives had divulged their fears to the doctor, and on the other hand if the doctor had been more skilful in his assessment of the case.

To look only at suicides is to observe the apex of the iceberg and to ignore the vast submerged portion which is so much greater. The figures in our practice show that as many people die from the hopeless inanition induced by severe depression as die by their own hand. They are nearly all senile depressions and what a dreadful end it is. In my experience depressive disorders are the com-

monest reason for suicide: but there are of course other causes. If the population of Ibstock is at all representative of the country as a whole, there must be some 180,000 chronic depressions in the community, a burden to themselves and everyone else. Acute treatable depressions will be even more numerous. This is a problem which needs to be tackled vigorously, as vigorously as death on the roads. It is, however, important to form some idea of the magnitude of suicidal risk in all depressed cases.

The suicidal tendency over a small series of 68 cases of depression was assessed on a seven-point scale; all kinds of depressed patients were included (Table 1). If these figures mean anything, then there is a suicidal risk in about 40% of cases and a major hazard in 16% of cases.

Table 1
Suicidal risk in a series of 68 consecutive cases of depression

Grade of suicide risk	1 *Nil*	2 *Death fear*	3 *Browned off*	4 *Death wish*	5 *Suicidal ideas*	6 *Attempted suicide*	7 *Suicide*
No.	5	5	29	18	10	1	0
%	7·3	7·3	42·7	26·5	14·7	1·5	
		57·3%			42·7% Suicidal risk		

If the suicide rate is to be lowered then non-psychiatric doctors must help as spotters, and the general practitioner bears the main responsibility. Not only must he be able to recognize the symptoms through their various disguises, but he must also be an approachable person and easy of access so that patients will come and discuss their problems. The depressed person more than any other type of patient tends to avoid the doctor. Very often he feels he is being neurotic and must pull himself together. He may feel his is a religious or moral problem and no medical matter at all. He may be worried to an extreme degree because he feels he is going out of his mind and is afraid to go near the doctor. Even patients who have been carefully handled over past episodes sometimes feel 'This time I will get over it myself'.

Not only must the family doctor be accessible to the patient, he must be equally approachable to relatives. After all, the family unit is the first line of defence and if only relatives can learn to discuss the worry of a husband or wife who has swung into a depressive mood, then perhaps we shall be able to get down to early treatment and so lower the suicide rate. This responsibility of the community is very important and we must all do what we can to educate the public.

It is pointless to spot depressions if the severest

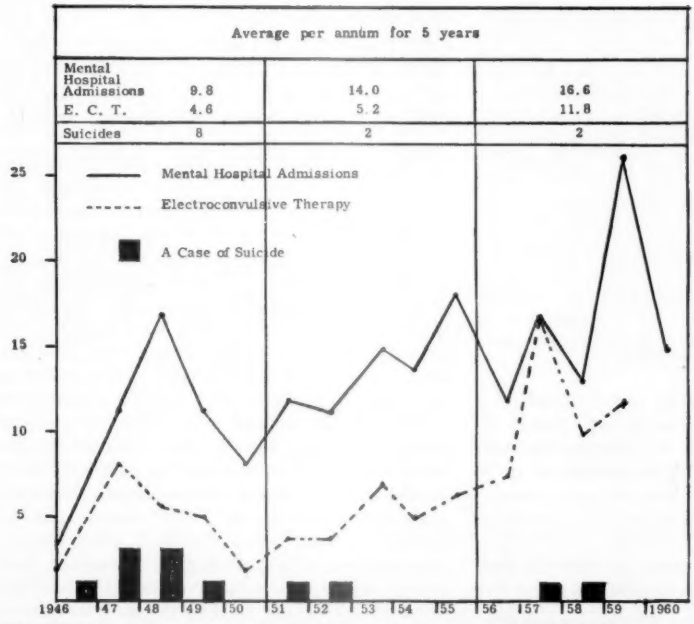

Fig 1 *Suicides, mental hospital admissions and E.C.T. Ibstock 1946–1960*

cases are not passed on to the experts. Free and easy access to psychiatric departments is essential. I have now worked in Ibstock for nearly fifteen years. I see some 40–60 depressed persons each year. Most people in the village now know I am interested in the subject and that they will get a sympathetic hearing. The number of actual suicides in such a compact community is too small to be statistically significant, but the figures are interesting and they are suggestive.

Fig 1 shows that over the years there is an increase in mental hospital admissions, and a rise in the number of patients who have had E.C.T. At the same time the suicide rate has fallen. In Table 2 the Ibstock figures are compared with those of the country as a whole. The low figures of the pre-war years show how misleading a small series of cases can be. The apparent fall in the suicide rate in Fig 1 is indeed no more than a straw in the wind.

Table 2
Suicide rate per 100,000 population

Years	*England and Wales*	*Ibstock*
1936–40	11·9	5
1941–45	8·43	10
1946–50	10·33	20
1951–55	10·42	5
1956–60	11·72	5
Average for 5 years	10·56	9·0

The problem of suicide is something we must all face. We who are outside psychiatry are in the forefront of the campaign. I believe that by being better diagnosticians, by being more aware of the dangers and disguises of depression, we in general medicine and in general practice can do more to lower the suicide rate than the psychiatrists themselves.

Suicide in Old Age

by Peter Sainsbury MD[1] (*Chichester*)

My purpose is to consider some social and psychiatric data on suicide in old people to illustrate how both kinds of information contribute to our understanding of suicide and to its prevention.

Suicide Statistics and Age

The suicide rates of both sexes increase with age. There is a sharp increase in middle age and a further increase with advancing age, the latter trend being much more pronounced in men than in women.

This rise in incidence of suicide with age is broadly the pattern found in nearly all those nations which publish suicide statistics (*Epidem. vit. Stat. Rep.* 1956). But pre-war China provided an instructive exception to this rule as the suicide rate of the old was less than that of the young. Ancestor reverence was then still customary so that the old person was not subjected to the loss of status and prestige which is usual in our culture (Yap 1961).

In the past fifty years the male suicide rates have been decreasing in most countries, but the decrease has been less in the old than in the young (Swinscow 1951). Female rates, on the other hand, have been increasing, especially in the elderly. When an attempt was made to account for the high suicide rates of the aged of 20 nations it was found that they were unrelated to the increase in the proportion of aged in their populations, and to the economic assistance provided by their old age pension schemes (Sainsbury 1961). Other social factors than the economic hardships of the aged were, therefore, thought to be determining their increase in suicide.

Suicide and Mental Illness

Batchelor & Napier (1953) diagnosed 10% of their attempted suicides aged 60 and over as having an organic dementia. I also noted an unexpectedly high incidence of organic dementia among suicides reported to a London coroner (Sainsbury 1955). Between 15% and 20% of those over 60 had signs both of intellectual deterioration and marked cerebrovascular changes *post mortem*.

Depressive illness is a more widely recognized precursor of suicide, and the probability of suicide in a patient with a psychotic depression is found to be much greater after the age of 40 (Robins *et al.* 1959). In one recent study (Batchelor & Napier 1953) 47% of suicide attempts aged 60 and over were diagnosed as having a depressive illness, and in another, 70% were found to be severely depressed (O'Neal *et al.* 1956). It is less easy to determine the incidence of depression in retrospective studies of those who have committed suicide. In 409 suicides in London, 55% of the middle aged and elderly were recorded by the coroner as depressed compared with only 40% of the younger cases. More recently Capstick (1960) concluded that 48% of 351 suicides over 60 were depressed. There is, therefore, a fair amount of agreement that pathological depression precedes suicide in about half the cases. The problem however, is what are the distinguishing features of the minority of endogenous depressions, estimated

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at about 14% (Robins *et al.* 1959), who will eventually commit suicide.

There is evidence that patients with depressive illness and suicides are distinct populations. The age- and sex-specific rates for depression and suicide (Table 1) show how different the two are. Their class distributions also differ. Nevertheless suicide and depression in later life are in fact associated, and this is clearly of real importance both from the point of view of recognizing the risk and of preventing suicide; but the crucial factors in the individual, in his environment and in their interaction which constitute the causal nexus of suicide, still need to be identified.

Table 1
Depression and suicide: rates per 100,000 (Registrar-General, 1959, 1960)

	Depression		*Suicide*	
Age	*Male*	*Female*	*Male*	*Female*
45–	56	22	91	16
55–	80	35	102	20
65–	58	43	72	22
75+	24	49	25	14

Physical Illness

Physical illness may predispose to suicide by restricting an old person's already limited activities, and in many other ways. But the physiological and biochemical effects of illness may also foster suicide because, of themselves, they may disturb consciousness and mood. MacKinnon & MacKinnon (1956) recently provided a very clear illustration of such a relation between suicide and endocrine physiology. They examined the endometrial sections of 23 women who committed suicide, and only one was found to be in the follicular phase of the menstrual cycle.

Social Factors

I have recently compared the incidence of personal stresses and crises supposedly precipitating suicide in the three age groups 20–39, 40–59, and 60 and over (Table 2).

Crises in personal relationships, in particular marital and family quarrels, preceded suicide most often in the young, less in the middle, and least in the old age group. The opposite obtained as regards physical illness, which was judged to have contributed to suicide in 10% of the young, 27% of the middle-aged and in 35% of the elderly. Both these differences are highly significant ($p < 0.001$).

Loneliness is another burden of old age. In London I found that the suicides were living alone to a significantly greater degree than were the population at risk. Moreover, suicides aged 60 and over were found to be living alone to a significantly greater extent than either the middle-aged or young. Similarly, *bereavement* preceded suicide significantly more often in the old-age group.

Wealth is associated with suicide; poverty is not (Sainsbury 1955). Also, no differences were found between the three broad age groups in the proportion of suicides attributable to *destitution*, *poverty* and *unemployment*; though lack of employment was mentioned as having contributed in 20% of elderly male suicides. In the other two age groups it was loss of employment, rather than lack of it, that apparently precipitated the suicide.

Retirement also appears to be associated with a rise in incidence of suicide, because male suicides reach their peak at 65–70. But women, whose working life is not subjected to the same abrupt change at this age, do not manifest the same sharp increase.

When the proportion of deaths from suicide in males in 30 occupations, sampling all socio-economic levels, were compared in the two age groups 20–64 and 65 and over, it was found that the proportion of deaths from suicide decreased on retirement in the higher status groups, but increased in the lower ones. The difference was significant (Sainsbury 1961). Suicide, therefore, tends to decrease after 65 in the higher social classes and increase in the lower ones. The former, it may be supposed, retire to more secure economic circumstances than the latter. This may not be the

Table 2
Incidence % of factors contributing to 409 suicides in three age groups

	Living alone	*Bereavement*	*Economic stress*	*Loss of employment*	*Personal relations disturbed*	*Physical illness*
Young 20–39	17	5	7	17	33	10
Middle-aged 40–59	23	9	17	22	11	27
Old 60+	39	16	15	21	8	35
	$p < 0.001$	< 0.02	NS	NS	< 0.001	< 0.001

NS = not significant.

crucial factor, however, as the higher social classes also tend to retire to opportunities for more varied interests and outlets and the evidence is, I believe, that it is these which protect the aged against suicide.

Recognition and Prevention

It has been observed that the seriousness of the intention to die is especially high in the suicidal attempts of the elderly (O'Neal *et al.* 1956) and of the physically ill (Hendin 1950). Intimations of suicide in the elderly, especially in the presence of physical illness, should therefore always be taken and dealt with at their face value. The prophylactic importance of correcting apparently minor ailments which limit the old person's independence should be emphasized.

Recent studies have indicated that about 70% of suicides were under medical care in the months immediately preceding death (Capstick 1960) and the same proportion, both above and below 60, communicated their intentions; though to their doctors less often than to their relatives (Robins *et al.* 1959).

It therefore seems that the little we do know about the clinical recognition of the potential suicide is insufficiently widely taught. The importance of depression in middle and late life has been stressed already, but what also needs emphasizing is that depression may masquerade as irritability, as over-concern about minor physical symptoms, or as a paranoid state; and that in organic confusional states a lethal depressive component is also often latent. In the more obviously depressed patient, sinister features include marked pessimism and hopelessness, delusions of worthlessness and of incurable disease. Above all it is always essential to discuss frankly with the depressed patient his attitude to the future, to dying, and to suicide.

Admission to hospital is advisable where there is a risk of suicide, but prison-like surveillance and restrictions may aggravate despair. I have recently examined the suicide rates of the resident population of our mental hospitals. From 1920–1947 they remained unchanged at about 50 per 100,000 (Stengel & Cook 1958). The advent of E.C.T. in the early 1940s was not accompanied by a decrease. During the 1950s, however, when a more liberal policy, including that of 'open doors' was introduced, the incidence of suicide in the resident patients decreased significantly. The last rate I have been able to calculate was 37 per 100,000 in 1956 (Registrar-General 1960). Perhaps a too zealous surveillance of the suicidal defeats its end.

Lastly, the prevention of suicide in later life will, I believe, depend to a considerable degree on social measures, such as providing for the basic economic needs of the aged and devising more elastic policy regarding the retirement of elderly people. More serious consideration needs to be given to planning retirement and to examining the needs of the retired elderly. I believe old people will continue to feel a useless burden, and therefore be suicide-prone until they have a real place in the community.

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Section of Anæsthetics

President R F Woolmer VRD FFA RCS

Meeting February 3 1961

Discussion on Fluid and Electrolyte Problems in Abdominal Emergencies

Mr L P Le Quesne (*London*)

Patients with an 'acute abdomen' may require resuscitation for a variety of reasons. In some instances blood loss or uncontrolled sepsis is the dominant factor. There is, however, another important group of patients, largely composed of cases of advanced intestinal obstruction or severe, general peritonitis, who are gravely ill as a result of an acute disturbance of their fluid and electrolyte balance. The problems presented by these patients, though they may well prove fatal if incorrectly handled, are usually soluble by quiet simple means: in effect, their treatment constitutes an exercise in applied physiology, and must be based on an appreciation of the main features of body fluid balance.

The disturbance in this group of patients is due to an acute depletion of their body fluids as a result of (*a*) an impairment of normal intake, (*b*) abnormal losses of intestinal secretions, as a result of vomiting and the accumulation of fluid in distended coils of intestine, and (*c*) the dislocation or sequestration of fluid into the peritoneal cavity and into the wall of inflamed loops of gut. The impairment of intake, which mainly causes water depletion, is relatively unimportant in this type of case, and the main factor in the depletion is the abnormal loss of fluid from the intestine. This loss, consisting of fluid containing sodium, leads to an extracellular depletion, with a diminution in circulatory volume. This in turn is aggravated by the sequestration of fluid into the gut wall and peritoneal cavity, as this protein-rich fluid derives directly from the plasma. As a result of these two processes, the critical disturbance is a depletion of the extracellular fluid volume, and particularly of its intravascular portion, this latter being further depleted in some cases by blood loss. Many of these patients present in peripheral circulatory failure, due to an inadequate circulatory volume. The immediate therapeutic problem is to decide whether this deficit of circulatory volume is due to sodium (salt) loss, plasma loss or blood loss, and then to administer the appropriate fluid. In some cases the deficit may be due to a combined loss of all three of these fluids. In reaching the decision as to which fluid is required, a measurement of the degree of hæmoconcentration is usually more helpful than an estimate of the plasma electrolyte concentrations. These patients may, in addition, have potassium depletion or a disturbance of their acid-base balance, but in the first instance these complexities can be neglected, and attention should be directed to restoring first, the circulatory volume, and then the whole extracellular fluid volume.

These patients will, almost invariably, require intravenous fluids, and the purpose of this treatment is, first, to replace the pre-existing deficit; secondly, to supply the patient's basic requirements of water and electrolytes; thirdly, to replace any continuing abnormal losses. These patients present a dynamic problem, which can only be managed satisfactorily by frequent assessment of their progress and response to treatment. In cases in which the initial deficit is large, this can and should be replaced rapidly in the first instance, at least until the circulatory volume has been restored. In this type of case there is no indication for the administration of steroids, at any rate until the circulatory volume has been restored and adequate steps taken to control sepsis. Whenever possible the deficit of body fluids should be replaced before operation is undertaken, because (*a*) operation on a patient with a body fluid deficit carries greater risks than on a patient in normal fluid equilibrium, and (*b*) the onset and development of the metabolic response to surgery increases the difficulty of accurately replacing the deficit. In cases in which operation is urgently indicated, every effort should be made to restore the circulatory volume before surgery is performed. Throughout their management these cases rarely require complex investigations, and in all cases

the most important factor in successful management is an accurate recording of the patient's fluid intake and output.

Dr P J Horsey (*Southampton*)

It is my purpose to consider the evidence which provides the answers to three simple questions: (1) What is the most appropriate replacement fluid? (2) How much should be given? (3) How quickly should it be given?

I shall consider only patients whose deficits of water and electrolytes have been rapidly incurred and shall not consider the special problems presented by infants and young children up to 18 or 24 months of age, or those of adults whose deficits have accrued over many days or even weeks such as are met, for instance, in cases of pyloric stenosis. The problem is to bridge the gap between knowledge of the elements of physical chemistry and the translation of that knowledge into active therapy at the bedside or in the operating theatre.

Patients with abdominal disorders who are described as being 'dehydrated' are inevitably suffering from water depletion, sodium depletion and potassium depletion.

The cations Na and K determine for practical purposes the osmolarity of the extra- and intracellular fluids respectively. The body fluids, both inside and outside the cells, are rigorously maintained in health at approximately one-sixth to one-seventh molar concentration: this means that for each milli-equivalent of these ions, some six to seven millilitres of water are retained in whichever compartment of the body fluids contains the ion in question. This they do half by virtue of their own osmolarity and half as a result of the osmolar attraction of their accompanying anion. As far as acute changes, such as we are dealing with, are concerned, there is a great deal of experimental and clinical evidence that water moves passively into or out of cells in response to solute concentrations of the intra- and extracellular fluid, which means the potassium content of the cells and the sodium of the fluid surrounding them (Edelman *et el.* 1958, Wynn & Houghton 1957, Conway 1957). There is now believed to be no sustained osmotic gradient between the two compartments but large changes in their respective volumes do occur as a result of shifts of water necessary to preserve identical concentrations of solute on either side of the cell membrane.

I will not consider potassium depletion at all, because there is general agreement that potassium should not be given in the initial stages of replacement. One is left, then, with water loss and sodium loss to diagnose and treat; there is no electrolyte 'imbalance' at this stage and this example of medical jargon is better avoided as it tends to discourage clear thinking by suggesting that it is a diagnosis in itself.

Water is distributed in an average adult of 70 kg so that the intracellular compartment contains rather more than double the volume of the extracellular fluid (ECF). The ECF is about 12–15 l., of which 3 l. is intravascular and comprises the serum water.

Pure water depletion – that is, water loss unaccompanied by significant amounts of sodium – does not occur in the type of case we are dealing with. It is, however, worth recalling its effects because it represents the reverse of the process which ensues when water, as 5% dextrose, is given intravenously. The water depletion is spread evenly through all compartments of the body fluids, which is of course a necessary consequence of the theory that isotonic conditions are always preserved across the cell membrane. It is important to realize that water depletion does not cause any sign or symptom of disordered function of the cardiovascular system until it has been established for several days. Black *et al.* (1944) deprived two volunteers of water for three and four days respectively. They found no rise in the hæmoglobin concentration or the packed cell volume (PCV) during this time, and said 'It may be inferred that there was little or no reduction in blood volume. These findings demonstrate that some highly efficient mechanism must have been at work to prevent such a reduction taking place because at the same time the volume of other fluid compartments of the body measurably declined'. This is in sharp contrast to the effects of combined water and sodium depletion which can cause cardiovascular collapse in a matter of hours. If 5% dextrose is given intravenously, it will distribute itself in the body in the same manner as water leaves it, i.e. one-third in the extracellular fluid and two-thirds in the cells.

There is selective depletion of the extracellular fluid when water loss is associated with sodium loss, as happens whenever fluid is lost from the gastrointestinal tract. The depletion is confined to the ECF and soon causes oligæmia.

If 140 mEq of Na are lost with each litre of extracellular water, which, turned round, is another way of expressing a loss of about 6 ml of water for each mEq of sodium, then there will be no change in the osmolarity of the extracellular fluid. Thus the serum [Na] will not alter however great the actual ECF deficit may be. If the patient loses ECF and then drinks and absorbs water, the relative Na depletion will then be greater than the water depletion. The effects of this can best be illustrated by considering the loss of 1 mEq of Na unassociated with any loss of water. Fig 1 shows a grossly over-simplified state of affairs – 2 mEq of Na, each holding 6 ml of water in the

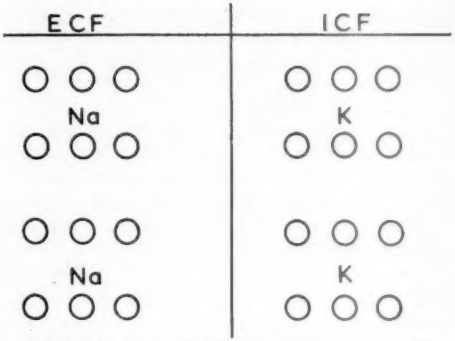

Fig 1 *Na and K represent 1 mEq of sodium and potassium ions. Each circle represents 1 ml of water*

ECF, and 2 mEq of K in the cells, also binding the same volume of water. If one mEq of Na is lost, but its water remains in the body, the water must distribute itself so that no osmolar gradient exists across the cell membrane. Fig 2 shows that 4 ml will go into the cells and 2 ml remain in the ECF, so that the tonicity of both compartments becomes $\frac{1}{3}$ molar instead of $\frac{1}{6}$. This also shows how a fall in extracellular sodium content of 50% is not reflected by a 50% fall in extracellular, and therefore serum, sodium concentration.

Thus sodium depletion causes extracellular contraction and tends to cause water to move into the cells. This is of more than theoretical interest because if a patient suffering from loss of ECF is treated with 5% dextrose or solutions as hypotonic as $\frac{1}{3}$ normal saline, the water will distribute itself predominantly in the cells. Isotonic or normal saline is therefore, volume for volume, nearly three times as effective in expanding the extracellular fluid and will allow none of its water to pass into the cells. If the amount of saline required is very great, a good case can be made for replacing part of the deficit with serum or plasma. Some may demur at this, but in these very ill patients I submit that it is both justifiable and desirable to use it. The only large-scale follow-up of serum hepatitis in this country was done in 1954 (*Lancet* 1954) on behalf of the Ministry of Health, the Department of Health for Scotland and the Medical Research Council. The results revealed an incidence of jaundice following the infusion of small pool plasma of 1 in 867 cases, less than one-thirtieth of that following the use of large pool plasma. The leading article in the issue of the *Lancet* publishing this investigation commented 'One can feel relatively safe in Great Britain in administering fresh whole blood, or plasma prepared from pools of 8–10 donations. These carry about the same risk – a risk that is very small indeed'. It certainly seems to me to be justifiable when the patient is in any case in grave danger of his life.

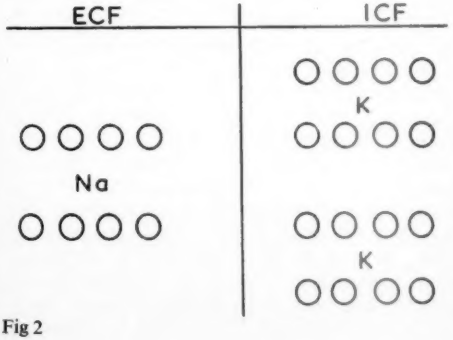

Fig 2

The answer to the first question then is that surgical patients who have become acutely dehydrated are suffering from loss of water, sodium and potassium. The immediate treatment is infusion of normal saline, with plasma if the deficit is severe.

The answer to the second question – how much fluid should be given – must be arrived at by considering evidence provided by the history, the clinical and the laboratory findings. Much of this is too well known to bear repetition and I will therefore only mention those observations which seem to me to have been most helpful.

Taking the history first, it is perhaps too obvious to stress that depletions of ECF of sufficient size to constitute a threat to life in their own right can and do occur unassociated with any history of abnormal losses. Patients with perforated peptic ulcers, or suffering from fæcal peritonitis as a result of a perforated diverticulum, may have three or more litres of fluid in their peritoneal cavities and yet give no history of abnormal losses. Such losses are likely to disappear down the theatre sluice, never to be recorded, as they should be, in the output column of the fluid balance chart. Every effort should be made to obtain an accurate history, but occasionally it will be completely misleading if taken by itself. The examination is more informative. One should remember that about 2 l. of extracellular fluid must be lost before any definite signs of dehydration appear and if obvious signs of disordered cardiovascular function are present, the deficit may well be double this. Signs which I find most helpful are coldness of the brow, nose, ears and, in extreme cases, of the tongue itself, and also a quite characteristic feeling of dryness when the fingers are thrust into the apex of the axilla. These signs are those of severe dehydration.

The blood pressure is a guide on which too much reliance is often placed. It gives a totally false sense of security if found to be above 100.

Thus patients whose blood pressures are, say, 110, are liable to be thought fair operative risks even if in obvious generalized vasoconstriction. Ten weeks ago a man of 68 who had vomited several times since a large inguinal hernia had become irreducible twenty-four hours previously, was operated on at Southampton. There were good reasons for being particularly careful to avoid overtransfusion and these, together with absence of vasoconstriction and a pressure of well above 100 before and during operation, resulted in his receiving only 1·2 l. of normal saline and 0·5 l. of 5% dextrose in the five hours between the start of the infusion and his death, four hours after operation. Blood, taken before operation, was examined the next morning with the following results: Hb 120%; PCV 68%; urea 87 mg%. These results speak for themselves – the packed cell volume is the highest we have seen in this type of case during the last year. At post mortem, grossly diseased coronary arteries were found and one cannot help feeling, with the wisdom of hindsight, that perfusion of such an arterial bed with blood, nearly three-quarters of which was red cells, may have been the precipitating cause of death.

Now for the help which the laboratory can provide. Blood may be very difficult to obtain from these collapsed patients and I now have no hesitation in withdrawing it from the brachial artery – a procedure which is unusually easy in just those cases from whom venous blood is most difficult to obtain. It also has the advantage of not requiring stasis, which tends to invalidate certain biochemical findings. Whenever I have done this, I have been struck by the apparent desaturation of the arterial blood – a finding which is perhaps of more than passing interest.

The laboratory can provide most valuable corroborative evidence of fluid depletion by estimations which can be done rapidly on 2 ml of blood. These are the Hb concentration, the packed cell volume or hæmatocrit and the serum protein concentration. Of these I would emphasize the Hb as being a very rapid determination requiring a minimum of skill to perform. Can we look to the laboratory for direct help in assessing the magnitude of the sodium deficit? The answer, unless one is prepared to withhold treatment while an estimation of the patient's total exchangeable sodium is performed, is 'No'. Knowledge of the exact serum sodium concentration is of no help whatever in determining the immediate treatment. If the history and examination support a diagnosis of sodium depletion and the serum [Na] is found to be 140 mEq/l., the treatment is rapid infusion of normal saline. If it is 130 mEq/l., the treatment is the same. Usually it will be between 135 and 140 mEq/l., and a raised blood urea level is a better pointer to sodium depletion than is the serum sodium concentration itself. I am not decrying serum biochemistry: the results from blood, taken before treatment is begun, form an invaluable base line subsequently, but if the blood is properly preserved, this can be done the following morning by a technician familiar with the estimation concerned. I commend to you the practice of taking blood from all dehydrated patients at least for estimation of the Hb and packed cell volume – if your experience is the same as ours, you will get some very salutary surprises of which I have already given one example.

Having established that dehydration is present, one is in a position to say that the patient is suffering from a depletion of at least 2 l. of his extracellular fluid. Hardy (1954) has given a n easily remembered rough guide to the probable size of the depletion:

Mild dehydration – deficit – 4% of body weight
Moderate „ – „ – 6% „ „ „
Severe „ – „ – 8% „ „ „

This gives added point to disciplining oneself to thinking in metric weights. If one is dealing with a patient guessed to weigh 8 stone, this on conversion to its metric equivalent becomes 50 kg. If the patient is thought to be moderately dehydrated, his deficit will be 6% of 50, which is 3 l. The interchangeability of weights and volumes is well worth the effort of learning to assess weight in kilograms.

This leaves only the third question to answer – how rapidly should the depletion of fluid, whose nature and volume is now assessed, be restored? The answer, I believe, is that half the assessed loss should be replaced with normal saline and it should be given quickly, by which I mean a ½-litre bottle every ten to fifteen minutes. This rapid infusion for such cases is advocated in a recent textbook of anæsthesia (Wylie & Churchill-Davidson 1960) in the following words 'When losses have occurred from the alimentary tract, it is perfectly safe to give 75% of the fluid as normal saline and it can be given quickly, i.e. 4 litres in one to two hours'. Having replaced half the estimated depletion with normal saline, with or without the addition of plasma or serum, one must then decide whether to go on with this fluid or to give electrolyte-free 5% dextrose. Here I emphatically agree with Mr Le Quesne that 'Every case must be considered as a therapeutic experiment, the response to treatment giving in many ways more information about the extent of the loss than the original assessment' (Le Quesne 1954). As long as there are signs of oligæmia, normal saline should be given: when circulatory efficiency has been restored, normal saline may well be alternated with 5% dextrose and the rate

of replacement must then be reduced. The larger the initial depletion, the more quickly should the first half be replaced and the more slowly should one aim to restore the second half. There are several reasons why severely dehydrated patients are liable to be given too little water and too little sodium.

Firstly, a serious attempt to estimate the size of the depletion is seldom made. Thus a patient in urgent need of rapid infusion may be described as being 'a bit dry' and brought to theatre with no drip, and no request for investigations. There is a diminishing margin of permissible therapeutic error – which applies equally to under-treatment as to over-treatment – as one progresses from mild cases, through moderate, to severely dehydrated patients. If a man with a 2 or 3 l. deficit is given 5% dextrose, or even if he is given no fluid at all, he will almost certainly survive. Because in the majority of patients the dehydration is not severe, the occasional one in whom it is tends to receive the same treatment but, resilient as the homeostatic systems of the body are, they are now outmanœuvred and the patient dies. The more depleted he is to begin with, the more obviously ill he will be, and the possibility that the proximate cause of death may have been inadequate water and sodium replacement may well not be entertained by either his pre- or post-mortem medical attendants.

Secondly, surgeons and anæsthetists naturally find the assessment and replacement of fluid loss very much easier when it occurs from an anatomical division of the body fluid, rather than from the physiological one which we call the extracellular space. They know that loss of 2 l. of blood will cause obvious signs of collapse and that these can be overcome by rapid infusion of 3 or 4 bottles of blood or plasma. They are used, in other words, to assessing leaks from a 5 l. tank. When faced with a leak from a 15 l. tank, they are reluctant to treble the volume of fluid given. The diagnosis and effective treatment of blood loss require experience: the recognition and restoration of extracellular fluid losses is much more difficult.

Thirdly, all who deal with surgical patients know that in the post-operative period there is diminished renal ability to excrete excess water and sodium. This is, not altogether happily, described as 'water and salt retention'. Although of great importance later, the fact that the patient is going to be unable to deal normally with excesses of water and sodium is no good reason for allowing the lethal effects of depletions of these substances to go untreated. If I may borrow the analogy of someone filling a bath, he who hesitates to give water and sodium on this score is like the bath filler who is afraid to fill the bath for fear that the overflow pipe is too narrow. The answer is to watch the bath as it fills and to turn off the taps before the level reaches the overflow.

Coller *et al.* (1945) and Limbert *et al.* (1945) are the authors of the two most frequently quoted papers which draw attention to post-operative œdema resulting from infusion of normal saline. Coller, in the first thirty hours following abdomino-perineal resections of the rectum, gave 5 patients nearly 4 l. each of normal saline. Limbert, describing 6 cases of resections of carcinoma of the colon, gave an average of 299 mEq Na a day for a week – some three-and-a-half to four times the amount now recommended. Such work was of value in stopping the common practice of routine infusion of normal saline post-operatively but must not be taken out of its proper context to prevent pre-operative restoration of water and sodium deficits.

The final reason is a fear that hypotension and circulatory failure may have caused renal tubular damage. A severely dehydrated patient is invariably oliguric, and may indeed have tubular damage, but this is an uncommon disorder and will only tend to be made more likely if his fluid depletion is not rapidly made good. No patient should be deprived of his chance of survival by being refused active treatment on this score. de Wardener (1960), in a slightly different context, likens this to refusal to throw a lifebelt to a drowning man for fear that it may hit him on his head.

Perhaps a deterrent more effective than any of these is the underlying fear we all quite rightly have of over-treatment. One knows all too well that a death resulting from excessive infusion will not pass unrecognized: if the patient dies with ineffective fluid replacement, the outcome will be readily ascribed to the underlying cause, but one is no less culpable than the other.

Mr Le Quesne has stressed that depletions should be corrected before operation if possible. Cases occur in which urgent surgery is essential and then Hardy's advice (1954) – restore the blood pressure, operate and continue treatment – has to be applied. Six months ago a child of 5 weighing 19 kg (just over 40 lb) was admitted to Southampton Children's Hospital. He was described as being 'an extremely ill, pale, collapsed, almost moribund child'. His radial pulse was impalpable and his blood pressure was unrecordable. A cut-down was done, and no blood could be withdrawn from his saphenous vein. He was given a very rapid infusion of normal saline and taken to theatre at 3·30 pm, when his blood pressure was 85/50. At operation the whole peritoneal cavity was full of pus as a result of a ruptured appendix, which was taken out. Between starting the infusion at 1 p.m. and 8 a.m. the following morning this child received 2·75 l. of isotonic fluid, which included one

bottle of plasma and contained about 450 mEq of sodium. At no time did there appear any signs of over-transfusion: the drip was taken down and his bowels opened on the third post-operative day, sixty-six hours after his admission.

This illustrates that young children can be treated just as energetically, having regard to their weight, as adults. His replacement represents the administration of considerably more than 10% of his body weight with isotonic fluids. Children of this age group are in danger of being treated with fluids and rates of fluid replacement appropriate to neonates long after the special handicaps of infancy are left behind.

These cases often occur at night: one is relieved to have got a living patient off the table. On his return to a general ward, responsibility for observing him devolves often upon a junior nurse. Several times in the last few months house surgeons have been summoned to such cases in the small hours of the morning because of cardiovascular collapse. On each occasion a noradrenaline drip has been started. Now I do not believe there is no place for this drug but I do most sincerely believe that far the most likely cause of relapse into circulatory failure in the first eight or twelve hours after operation is inadequate water and sodium replacement: if there is no evidence of central circulatory failure, such as may be caused by coronary occlusion or a large pulmonary embolus, the only way to prove this is to give ½–1 l. of saline or plasma rapidly and to stay with the patient while it is given. There will usually be obvious improvement within half an hour, and there is then no place for noradrenaline. If no improvement results, the rapid infusion must be stopped and resort be had to vasoconstrictor drugs. This, in my experience, means that the patient has passed the point of no return.

Finally, I stress that none of this is new knowledge. Thus, in 1924, two American surgeons (Gatch & Durman 1924) in Detroit, reporting 262 cases of appendicitis, said 'We feel that the administration of an adequate amount of fluid is the single most important part of the treatment. The circulatory failure in the great majority of cases is due to dehydration. The heart is a perfectly competent pump but the circulation fails through lack of sufficient fluid to be kept moving. A healthy young patient can withstand a whole lot of peritonitis if he is given plenty of fluid'.

Going back to 1832 – well before the invention of the hypodermic needle or the discovery of anæsthesia – one finds that the different effects of infusion of saline and infusion of water were already appreciated. In a book entitled 'The History of the Contagious Cholera' is written:

'In Leith, the quantity of saline matter has not been so large as in Edinburgh, where the mixture in use consists of 120 gr. of common salt, 40 gr. of carbonate of soda, dissolved in 5 lbs. of water . . of this 5 lbs. are injected into a vein in the arm in the course of 30 minutes; and 10 lbs. are frequently injected at this rate without stopping.' And later: 'a fair trial has been made of warm water without the salts but the effect was obviously less marked and much less lasting' (Kennedy 1832).

One year earlier, the *Lancet* (1831–1832) published a leading article which reviewed the whole practice of intravenous saline treatment:

'In one case, nearly 7 lb were at once thrown in to the median basilic vein, and in 9 hours 15 lb were infused . . . It teaches us how boldly we may proceed when certain and scientific data are before us, and it thus dispels the all-but-cowardly timidity which has hitherto prevented the principles of the treatment in question from being carried into effect . . . The quantity of water to be replaced is therefore immense, and bears no relation to the presumed quantity of blood which the human body naturally contains.'

It is up to each one of us who plays any part in the management of these very ill patients to ask himself if this knowledge is indeed being applied a hundred and thirty years later.

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Meeting January 6 1961

Dr J J L Ablett read a paper entitled **Observations on the Management of Tetanus, with Special Reference to the 'Paralysis Regime'.** The paper was illustrated by a film.

Section of Orthopædics

President A L Eyre-Brook MS

Meeting October 4 1960
(continued from January 'Proceedings' p. 74)

Cases

Léri's Pleonosteosis

P M Yeoman MB FRCS

S R, female, aged 16, was noted at birth to have lack of suppleness of the fingers; a contracture of all the fingers was noticed at the age of 5 years. One year later she complained of paræsthesiæ of both thumbs on awakening each morning; this persisted intermittently for two years and was associated with progressive weakness, and later contracture of both thumbs.

On examination: An intelligent girl with a broad face, flattened bridge of the nose and normal stature. The fingers were contracted at the proximal interphalangeal joints, the thenar muscles were wasted and there was a severe contracture of the first clefts (Fig 1). The wrists were thickened; the elbows lacked 20 degrees extension and the left shoulder lacked 30 degrees external rotation. The feet were broad; there was a mild cavus deformity and the toes were clawed. There was no relevant family history.

Investigations: Radiograph of the fingers (Fig 2) showed broad phalanges. *Nerve conduction time:* Right median nerve at the wrist to abductor pollicis brevis muscle 20 msec (normal 3 to 5 msec). *Sensibility:* Two-point discrimination, pulp of right index, 8 mm. *Muscle biopsy:* Abductor pollicis brevis showed severe atrophy of muscle fibres and degeneration of conducting elements. The appearances suggested an atrophy of neural origin.

Comment: Watson-Jones (1949) reviewed the literature and reported 4 cases of Léri's pleonosteosis; 1 patient had bilateral compression of the median nerve in the carpal tunnel and bilateral plantar digital neuromata. This was the first published description of such a complication.

The case recorded here is very similar and illustrates the insidious nature of median nerve compression at the wrist in a child afflicted by this rare condition; unfortunately the best time for decompression of the median nerve was ten years ago. The problem is now twofold; firstly, to prevent further loss of sensibility in the fingers; secondly, to restore active opposition of one or both thumbs, if the contracture of the first clefts can be released.

Fig 1

Fig 2

Acknowledgment: I should like to express my thanks to Mr H ' Seddon for permission to record this case.

REFERENCE Watson-Jones R (1949) *J. Bone Jt. Surg.* **31B**, 560

The following cases were also shown:

Non-Specific Granuloma of Bone
Mr N E Shaw (for Mr Donal Brooks).

Coxa Vara with Protrusio Acetabuli. ? Morquio.

? Rheumatoid Arthritis in a boy aged 13
Mr E H Hambly.

Meeting November 1 1960

Papers

Transthoracic Surgery of the Spine

by Harold J Richards FRCS (*Cardiff*)

The surgery of the vertebral bodies is not new, and as early as 1906 Müller described a retroperitoneal approach to the anterior surface of the lower lumbar vertebræ for the purpose of draining a tuberculous abscess.

In 1951 Osmond-Clarke carried out an anterior fusion of the bodies of the cervical vertebræ.

The surgery of the bodies of the dorsal vertebræ had been rendered feasible by the improvement in anæsthesia and post-operative care.

Since 1952, following a period of observation at a thoracic unit, I have used a routine thoracotomy through an intercostal space, or by a rib resection, as a standard approach for the surgery of the bodies of the dorsal vertebræ.

Cases 1–4 are described to illustrate the conditions treated by this method.

Congenital Abnormalities

Case 1 J W, aged 5½

This boy had no obvious abnormality of his back at birth but over the past two years his mother had noticed an increasing deformity, and in the past six months, the boy had complained of pain in his back radiating down the back of both thighs as far as the knees, and this had interfered with his ability to play games. He had also become unsteady on his feet and fell frequently. An X-ray of his spine showed a congenital wedge vertebra (Figs 1A & B).

Through a routine thoracotomy, the disc above and below the wedged vertebra was excised posteriorly with a view to limiting growth of this part of the body, in the hope that it would minimize the deformity. At the same time, a strut bone graft was placed between the two arms of the kyphus.

An X-ray taken five years later (Figs 2A & B) shows that there has been no increase in the deformity, and it is just possible to see the site of the strut bone graft.

Following operation, the boy made an uneventful recovery, has had no further symptoms and takes part in all the usual boyish activities.

Von Lackum & Smith in 1933 reported enucleation of the bodies of these congenitally deformed vertebræ, and Wiles in 1951 reported complete excision of them. All the authors recorded a relentless progression of the kyphosis following operation. This case is not as severe as those reported by Von Lackum & Smith and Wiles, but up to the present the deformity has not progressed.

Tuberculous Lesions

Case 2 V C, aged 23

At the age of 15, this girl was in hospital with a tuberculous lesion of the dorsal spine and was treated by immobilization on a plaster bed for two years, and had two courses of chemotherapy. Following this, she wore a special support but the back had never been comfortable and the deformity had gradually increased. Six months prior to being seen she had had severe pain in the lower dorsal region of her back which radiated round the ribs and she had lost weight. X-rays (Figs 3A & B) show a tuberculous lesion involving the dorsal spine, with a large paravertebral abscess. Figs 4A & B, taken eight years later, show that there has been further destruction of the bodies and the paravertebral abscess is larger. This suggests that the original abscess shown in the first X-ray (Figs 3A & B) has been present for eight years.

A left thoracotomy was carried out and a large paravertebral abscess was drained through multiple incisions placed between the segmental vessels. Some bone chips were then inserted. It was not possible to get round to the other side of the vertebræ and six weeks later a right thoracotomy was carried out and a moderate-sized abscess was found on the other side; it was drained and bone chips were again inserted. Figs 5A & B show the spine three years after operation. The abscess has subsided and the bone chips have become incorporated. She is completely free of symptoms, is now able to do her own housework and is anxious to have a baby.

Observation of the X-rays will show that scalloping or hollowing out of the vertebræ developed over the years, and I think this is due to the varying tension applied to the abscess during respiration. This is supported by finding at operation that, when the abscess is incised, the pus gushes out with each inspiration.

A similar procedure has been used for the drainage of an acute tuberculous abscess and also for removal of sequestra from the bodies of involved vertebræ.

In all these cases the patients have been given a course of anti-tuberculous drugs, and following operation have been immobilized in a plaster of Paris bed for three months followed by the wearing of a plaster of Paris jacket for a further three months.

Hodgson & Stock (1956) have reported using the transthoracic approach to the dorsal spine for tuberculous lesions and they are in favour of division of the segmental vessels and of a linear incision into the abscess. I think that the less the blood supply in the region of a tuberculous lesion is interfered with the better, and that it is preferable to use bone chips for grafting as they are

Fig 1A *J W, Case 1, 12.11.55*

Fig 1B *J W, Case 1, 19.11.55*

Fig 2A *J W, Case 1, 2.1.60*

Fig 2B *J W, Case 1, 2.1.60. The arrows indicate top and bottom of bone graft*

Fig 3A *V C, Case 2, 9.5.49*

Fig 3B *V C, Case 2, 16.6.50*

Fig 4A *V C, Case 2, 20.4.57*

Fig 4B *V C, Case 2, 20.4.57*

Fig 5A *V C, Case 2, 19.6.60*

Fig 5B *V C, Case 2, 19.6.60*

Fig 6A *B W, Case 3, 2.6.56*

Fig 6B *B W, Case 3, 2.6.56*

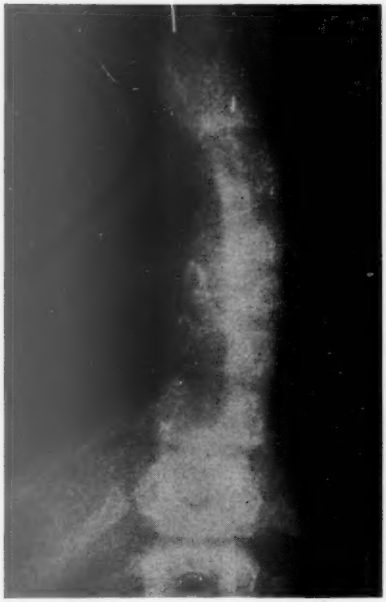

Fig 7A *B W, Case 3, 18.9.60*

Fig 7B *B W, Case 3, 18.9.60*

Fig 8A *C W, Case 4, 11.1.60*

Fig 8B *C W, Case 4, 23.7.56*

more likely to resist infection and to become incorporated than is a strut graft.

Destructive Lesions

Case 3 B W, aged 9

At the age of 4, this girl developed a destructive lesion of D 6 and D 7 with evidence of pressure on the spinal cord. A wide laminectomy was carried out and an extradural tumour found. This proved to be a lymphoblastoma and post-operatively she was given a course of deep X-ray therapy. She made a good recovery and wore a spinal support for two years. This, however, failed to prevent the development of a kyphosis, and four years after the original operation she was becoming paraplegic. An X-ray at this time (Figs 6A & B) showed a scoliosis and a marked kyphosis of the dorsal spine.

A right thoracotomy was carried out; a biopsy was taken from the site of the original tumour, and then a strut bone graft, using a piece of rib, was placed between the arms of the kyphus. She made an uneventful recovery. The biopsy showed no evidence of recurrence of the tumour and an X-ray taken three years after the bone-grafting operation shows that the graft has become incorporated and is expanding at its upper and lower ends and that there has been no increase in the kyphosis (Figs 7A & B).

This girl is well in herself but still has a slight increase in the tone of the muscles of the right leg.

Fig 9 *C W, Case 4, 12.10.60*

Scoliosis

Case 4 C W, aged 11

This girl had diastematomyelia associated with a dorsal scoliosis and a straight spine when viewed from the side (Figs 8A & B). The scoliosis had gradually progressed over the years. A laminectomy was carried out over the level of D4 to D11 and the spike of bone which had split the spinal cord was removed from the floor of the canal.

Following this operation, the patient and her parents insisted that the scoliosis be corrected and the only way to maintain the correction was to fuse the dorsal spine.

In view of the wide laminectomy, epiphysiodesis through a right thoracotomy was carried out. The discs between D4 and D10 were excised on the convex side and bone chips packed into the resulting gaps. She made an uneventful recovery, two months later the traditional posterior spinal fusion was carried out between D4 and C1 and D10 and L1 (Fig 9).

This is not recommended as a procedure for the fusion of a primary curve in scoliosis, but in view of the wide laminectomy there was no alternative to epiphysiodesis for the fusion of this part of the spine.

I think it will be appreciated that the transthoracic approach to the bodies of the dorsal spine has rendered feasible the treatment of some difficult conditions.

This surgical treatment should be carried out in conjunction with a thoracic surgeon as it can be, on occasions, a difficult operation, and I would like to express my gratitude to my thoracic colleagues at Sully Hospital who have helped me in this work.

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DISCUSSION

Mr A T Fripp (*London*) said that his experience of the transthoracic approach was limited to the treatment of spinal tuberculosis. He had found this approach the best for the great majority of cases from the 4th thoracic to the 1st lumbar vertebræ. It gave excellent access to the lesion. It was possible to drain the abscess on both sides of the spine and to expose the dura anteriorly. Therefore it was also suitable for many cases of paraplegia, but was contra-indicated when the kyphosis was severe.

He disagreed with Mr Richards that it was necessary to open both sides of the chest, as the far side would be adequately exposed from the operation side.

Mr A Graham Apley (*Pyrford*): **Transthoracic Approach in the Treatment of Scoliosis**

The value of a transthoracic approach in the surgery of spinal tuberculosis has been discussed. Attention is drawn to a similar approach in the treatment of infantile scoliosis. Collaboration with a thoracic surgeon

is essential and, with Mr Meredith Brown, a small series of operations was commenced in 1954; the children selected for operation were those with a severe curve and in whom the standard methods of treatment had failed. The operation had been used in only a few patients and for only a few years, so that we are not in a position to assess its value. It must be emphasized that as a method of treatment we are still only at the stage of exploring its potentialities; but, as an approach to the scoliotic spine, we have no doubts and we are enthusiastic about its possibilities.

The essence of the operation is to try to control vertebral growth; that is, to prevent growth on the convex side of all the vertebral bodies constituting the primary curve, while still allowing growth on the concave side.

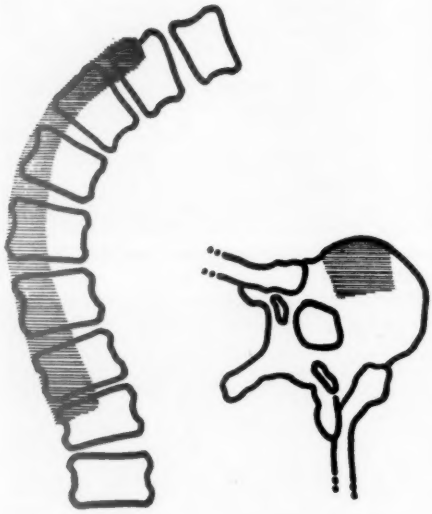

Fig 1 *The shaded area shows the extent of the gutter from which bone and cartilage are removed*

In 1951 Nachlas & Borden showed that stapling the vertebral epiphyses was capable of producing scoliosis in dogs, as well as of correcting the deformity so produced. Stapling for congenital scoliosis was described in 1954 by Smith *et al.*, but, as was shown by the discussion which followed this paper, many surgeons doubt whether stapling by itself can exert enough force to correct a severe scoliosis in the young. In 1960 McCarroll and Costen described 4 cases of attempted treatment of scoliosis by unilateral vertebral epiphyseal arrest; they failed to control development of the curve, but they dealt with only three or four vertebræ and not with the entire primary curve.

Technique

(1) The patient lies in the lateral position, with the convex side of the primary curve uppermost. The rib which arises from the apex of this curve is excised. The parietal pleura is incised along the length of the skin incision, and a rib spreader inserted. As the lung collapses, the view of the spine displayed is quite astonishing. Almost at the very surface of the wound the vertebral bodies present themselves, and several bodies are readily available for operative procedures. To those who have never approached a scoliotic spine in this way, the ease of access is a revelation.

(2) The parietal pleura is now divided again, this time more posteriorly, along the line of those vertebræ which it is proposed to fuse; that is, the vertebræ which constitute the primary curve. In this area the intercostal vessels are tied and divided between ligatures.

(3) A longitudinal gutter is next cut along the spine. In length the gutter extends upwards and downwards from the apex of the curve, until it includes the whole of the primary curve; in width the gutter is one-third to one-half an inch, according to the size of the bodies; and in depth it is about half the diameter of the vertebræ (Fig 1). Bone, cartilage and disc substance are scooped out until there is one continuous groove throughout; the epiphyseal (growth) cartilage is of necessity removed as part of the scooped-out material. If more access to either end of the primary curve is required, the rib spreader is taken out, and a second incision made in an appropriate nearby intercostal space; through this the rib spreader is reinserted.

(4) The bone which has been cut away is denuded of cartilage and packed tightly into the bottom of the gutter. On top of these chip grafts the excised rib is placed. In order that cancellous bone should be in contact with cancellous bone the rib is first split along its entire length; the split halves are easily bent to fit accurately into the gutter. A bone graft is thus fashioned which holds the chips in place.

(5) The pleura is sutured over the graft and the anæsthetist re-expands the lung. These measures are sufficient to hold the rib in place. The incision is closed, leaving a rubber tube connecting its cavity with an under-water seal. Muscle and skin are then sutured and the tube is removed in forty-eight hours.

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ACTH in Treatment of Lumbar Disc Prolapse

by A Naylor FRCS
and R L Turner MD (*Bradford*)

Less importance is now attached to trauma as a major basic factor in the production of intervertebral disc herniation. The probable role of the fluid content of the nucleus pulposus has been stressed previously (Charnley 1952, Naylor 1951, Naylor & Smare 1953, and Bush *et al.* 1956) and the possibility of an endocrine factor initiating the sequence of changes leading to an increased fluid absorption by the nucleus pulposus, and hence rise in intradisc tension, was suggested by us as a

possible factor in the development of the disc syndrome (Naylor 1951, Naylor & Smare 1953). Hirsch (1951) reproduced typical low back pain by raising the pressure within intervertebral disc by injection of saline into the nucleus pulposus. Scott's report (1955) – that in voles subjected to 'stress' and therefore increase in adrenocortical activity, as induced by fighting, the volume of the nucleus pulposus was greater than in the control animals – appears to support our hypothesis. Feffer's report (1956) on the beneficial effect of intradisc injection of hydrocortisone in 67% of a series of 55 patients suffering from lumbar disc prolapse, whilst indicating direct action of the hormone rather than any general disturbance of water balance, serves to support an endocrine hypothesis but is contrary to what one would anticipate from Scott's work.

In an endeavour to examine the possible effects of changes in general or local water balance in lumbar intervertebral disc prolapse, we undertook an investigation of the effect of administration of ACTH in such cases. ACTH was used because of its known effect on both mesenchymal tissues and the distribution of water and electrolytes between various fluid compartments of the body.

The present report concerns the effects of ACTH administered intravenously to 38 patients suffering from lumbar intervertebral disc herniation.

Selection of Cases

Only those in whom the diagnosis of lumbar disc prolapse could be made with certainty and who were experiencing considerable pain, limitation of lumbar movement, with a leg-raising test at 60 degees or less from the horizontal, were admitted to the trial. Previous history of peptic ulceration or hypersensitivity to ACTH protein excluded some patients from investigation. Of 38 patients submitted to trial treatment, 31 were males and 7 females, whose ages varied between 16 and 61 years. Over half the patients were between 26 and 40 years of age.

Experimental Method

Following admission to hospital, the patient's clinical condition was re-assessed after a period varying from ten to fifteen hours' bed rest, i.e. overnight, no significant change being found in the clinical signs and symptoms of any patient. Skin tests for ACTH protein sensitivity were made, blood pressure recorded and serum electrolyte estimations made. An intravenous drip was set up using an arm vein and a fixed volume of fluid, i.e. 2 litres of 5% dextrose in water, was given to each patient over a period of forty-eight hours. 1,000 units of heparin and the requisite quantity of ACTH were added to the volume of fluid administered. The dosage of ACTH varied from nil to 400 i.u., the presence or absence, and amount, being unknown to the clinical observer. The hospital pharmacist, who made up the solutions, withheld the details of dosage until all the results of the series had been examined and tabulated.

The patient was kept on a salt-restricted diet whilst the oral intake of fluid was limited to $1\frac{1}{2}$ litres per day. Movement within the restrictions imposed by the intravenous drip was allowed. The straight-leg-raising test, blood pressure and subjective symptoms were reassessed after twenty-four hours and forty-eight hours when the infusion was discontinued. Blood electrolyte examination and complete clinical reassessment were made immediately after cessation of administration of the intravenous drip infusion and all results recorded refer to that period. Subsequently all patients had a lumbar plaster jacket applied, were discharged from the ward, and followed up at intervals for at least three months.

Results

The results obtained after forty-eight hours' intravenous drip infusion and before application of a plaster cast are classified as follows:

Nil:

Slight improvement: a little symptomatic relief but no objective improvement

Moderate improvement: considerable symptomatic relief and objective improvement short of complete relief

Complete symptomatic relief: complete freedom from both sciatic and lumbar pain

No patient showed an exacerbation of symptoms or was made worse in any way by the transfusion.

Complete symptomatic relief was obtained in 12 patients, of whom 2 were female, whilst 12, of whom 2 were females, showed moderate improvement as defined above. 8 were only slightly improved and no change was noted in 6. Of the 24 patients who obtained complete or moderate relief of their symptoms all but one have remained free from pain during the subsequent period of observation. The solitary exception relapsed within three days of the cessation of administration of ACTH, but subsequently obtained complete relief by a further administration of the hormone for forty-eight hours. One patient obtained complete relief with a nil dosage, but it was notable that this patient gave only a short history, symptoms being present for seven days prior to initiation of treatment. No relationship between the patient's sex and response was apparent. Of the cases treated the symptoms were of spontaneous onset in all but three. Three cases developed following injury and of these two were

only slightly relieved and one moderately improved by therapy. Within the dose range employed, the effect on the symptomatology is not closely related to the total dose of ACTH administered. Whilst improvement in physical signs was noted in those responding favourably to ACTH the subjective relief, i.e. diminution of pain, was more marked than one would anticipate from the change in physical signs. Relief of symptoms and signs usually became evident during the first twenty-four hours of administration of the hormone.

The serum electrolyte before and after therapy showed no consistent changes and using the Student's 't' test, statistical analysis showed no significant change. There was no significant effect on the blood pressure readings.

The patients were divided into five groups on the basis of the amount of ACTH administered, and the clinical result, to facilitate statistical analysis, was awarded an arbitrary score. An analysis of variance then carried out failed to demonstrate a significant difference at the 5% level between the groups who had ACTH and the group who had intravenous glucose alone.

Comment

ACTH by its stimulatory action on the adrenal cortex may theoretically be expected to have two mutually antagonistic effects on the symptoms arising from lumbar disc herniation. Thus, if the disc participated in the general retention of water that occurs in the body following prolonged administration of ACTH we might anticipate an exacerbation of symptoms. On the other hand the known beneficial effect of ACTH on mesenchymal inflammations and degenerations would tend to alleviate the disc syndrome. Although in this series no evidence for the first effect was noted, the failure to demonstrate a clear-cut beneficial effect of ACTH may be due to the interplay of these two factors in any one patient. In those patients, who showed complete or marked relief, approximately two-thirds of the series, the beneficial effect was evident within twenty-four hours and well developed at the end of the forty-eight-hour treatment period. Such a period of very incomplete bed rest, even allowing for the preceding overnight stay, would of itself be insufficient to account for the marked and rapid improvement, especially as many had been treated ineffectively with bed rest by their general practitioner prior to reference to hospital.

The failure to demonstrate any significant change in the mean electrolyte concentration of those patients receiving ACTH and the rapidity with which the relief of symptoms and signs was apparently obtained, would seem to indicate that no major general shift of water between the various compartments of the body had occurred. It should be noted, however, that in this preliminary survey no attempt was made to measure plasma volumes or the volume of extracellular fluid. Such changes might mask changes in electrolyte concentration and need further investigation.

Although the results of the statistical analysis do not warrant the adoption of ACTH as a method of therapy for the treatment of lumbar disc herniation, the clinical effects obtained with ACTH in this small series are of considerable theoretical interest. It should be apparent from the above that they offer support to the theory that herniation of the nucleus pulposus represents some alteration in the disc's capacity for water imbibition. The position would appear to warrant further trials with other agents known to influence cell permeability and the exchange of water and electrolytes across biological membranes.

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Intraosseous Venography Using Cine Radiographs [*Summary*]

by R G Smith MB FRCS (*Sydney*)
From St George's Hospital, London

Using an image intensifier it is possible to take cine radiographs to show the fate of radio-opaque media injected into the medullary cavity of bone. Under general anæsthetic with fluoroscopic screen control a troca and cannula of external bore 3 mm can be readily inserted into the medullary cavity. After a suitable test injection, 10 ml of 60% Urografin, sterilized by autoclaving at 15 lb/sq in. for 20 min, is injected in 10 sec and filming commenced immediately.

This procedure is less cumbersome and more frequently successful than the routine still radiographic venogram and has the advantage of producing a dynamic record of the fate of the injected dye rather than a simple anatomical display of the vessels.

A film was shown to demonstrate the cine venogram of the hip region before and after intertrochanteric myelotomy.

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A film illustrating **Posterolateral Fusion of the Lumbosacral Spine** was shown by Mr David Le Vay (*London*).

Section of General Practice

President L W Batten MRCP

Meeting December 21 1960

Discussion on the Right Patient in the Right Bed

Dr G F Abercrombie (*London*)

'There's no place like Home'. Many general practitioners are making great efforts to keep and treat patients in their own homes, and the antibiotics and other modern drugs are of immense value in aiding this. Social conditions, however, work against us, and we are all familiar with the difficulty of obtaining adequate nursing and domestic help, particularly for old people who live alone.

Surgeons too have changed their methods, for I recall, as a boy, having four quite different operations in my own small nursery, none of which would now be undertaken by any surgeon outside the walls of a hospital or a nursing home. The surgeon's personal convenience is now the primary consideration and it must be admitted that he no longer has time for domiciliary operations and the necessary after-care. Moreover, so much preliminary investigation and so much highly specialized apparatus is now required for any major operation that transfer to hospital for surgical emergencies and serious accidents is inevitable.

My impression is that patients who suffer a coronary occlusion are best kept at home, until shock has passed. To move such a patient by ambulance, perhaps only a mile or two, to a strange environment, in cold, wet or foggy weather, seems to me to add a small extra hazard which may be fatal.

Miscarriages are a considerable anxiety in unsuitable surroundings. It is often difficult to be sure whether the abortion is complete, the risk of infection is great and in the most important, the criminal case, it is very unlikely indeed that the doctor will be able to learn the true facts. More and more of these patients are being sent to hospital, where observation can be continuous and where action can be taken.

Obstetrics: Maternal mortality and the neo-natal death-rate are now so low that the utmost vigilance is required to reduce them still further, and it is authoritatively recommended that all primigravidæ, all grand multiparæ, all those with a present abnormality or a past complication should be admitted to hospital for delivery. Added to these must be a large number whose home conditions are not suitable, by modern standards, even for a normal confinement. The present estimate is that 70% of confinements should take place in an institution, and that percentage will most certainly increase; but I have never been able to understand why very many of these patients should not return home, if home is at all suitable, within forty-eight hours. It has been demonstrated, notably by Theobald (1959) in the Bradford Experiment, that, given good co-operation all round, the risks incurred by mother and baby are negligible, and that very few mothers indeed have to be readmitted. I stress forty-eight hours, for by that time the obstetric hazards are at a minimum, and lactation has not begun. Breast feeding is far more likely to be successful in the natural home environment under the eye of a single adviser, midwife or general practitioner. The right patient is in the right bed, if in hospital for delivery; but in the wrong bed, if in hospital for the puerperium.

In general, where the patient and the doctor have a choice, the choice of right bed is dependent upon a number of extraneous factors. There are still institutions which keep their opinions so strictly to themselves that I suspect they are original members of the S.S.U.I., the Society for the Suppression of Useful Information. The chosen hospital should not be so far from home that visiting by relatives and friends is unduly time-wasting. A previous happy experience in a particular hospital is a reason for return to that hospital, and to the care of the same consultant. It is deplorable that an 'old' patient, and here I put 'old' in inverted commas having in mind those whose disease is mortal, should be turned away from an institution in which he has confidence. It has often seemed to me that the decision, whether

to admit or not to admit, is in the hands of very junior medical men or women, who have neither the experience, nor the authority, nor indeed the humanity, that the occasion demands. The old Manchester diagnosis, K.O.H., Kindness of Heart, should never be forgotten. It is common knowledge, too, that in emergencies of this kind, where the original hospital cannot, or will not, admit, other hospitals are very reluctant to do so and to embark afresh on the investigations which have already been done elsewhere.

I shall say nothing of the nursing staff, except to quote Sir Alan Herbert:

> 'I like them fluffy, not huffy or stuffy,
> I like them fluffy with no brains at all.'

Urgent admission to hospital in the metropolitan area of London may be achieved by several methods.

(1) If an accident occurs in the home which in the opinion of the general practitioner requires treatment in hospital, he may dial 999, summon an ambulance and despatch the patient, with an explanatory note, to the nearest suitable hospital.

(2) Urgent cases may be transferred to hospital on direct request, and where the doctor is on good terms with his local hospital, with mutual trust, this is beyond doubt the best method.

(3) A doctor may arrange a domiciliary consultation with the idea of obtaining admission for his patient to hospital, not 'immediately', but without undue delay. This method savours of jumping the queue, and some consultants will not come out to such consultations, for fear that they will be embarrassed thereby. I personally regard the method as perfectly legitimate, provided the doctor is prepared to play the game fairly. He should be in genuine doubt whether his patient should be sent into hospital, and if so, how soon. This is the problem the consultant is invited to solve and he must accept some of the responsibility for the decision taken. If the patient may safely remain at home under observation, well and good; but if he ought to be sent into hospital promptly, then priority is established, and jumping the queue is right and proper.

(4) About 65,000 cases a year in London are admitted through the Emergency Bed Service, which is a department of King Edward's Hospital Fund and acts as an agent for the four metropolitan regional hospital boards. It was designed to save the time of the busy general practitioner by doing his hospital telephoning for him, and it is his highly skilled and specialized secretary. Those whom it succeeds in placing have very little choice of hospital. The doctor in his application may state a preference, which will be implemented, if possible. Hospitals often ask for particular types or manifestations of disease; enthusiastic

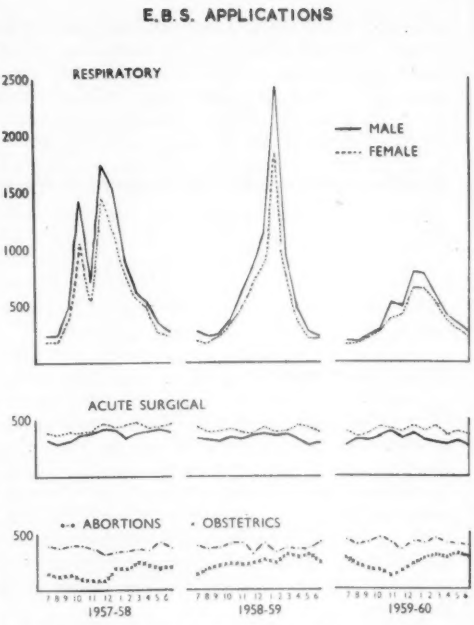

Fig 1 *Emergency Bed Service applications: seasonal variations*

house surgeons have been known to say that they have an empty bed or two, and would like an acute abdomen. E.B.S. will oblige if it can, but by and large the patients must go where they are sent. On the whole, however, E.B.S. has such a remarkable store of local knowledge that it is seldom that a patient will find himself in the wrong bed.

The work of the E.B.S. is subject to very considerable seasonal variations (Fig 1). Here, in graphic form, are the applications made in the last three years from July 1957 to June 1960, divided into male and female.

Acute surgical cases amount to a steady average of about 800 a month, with, as might be expected, more women than men. By contrast, the seasonal variation in the respiratory group is enormous, and men always outnumber women. Fig 1 shows first the epidemic of Asian influenza in October 1957, followed by another influenza epidemic in January and February 1958. Just one year later, there was an even more serious epidemic, which strained the resources of E.B.S. and of the hospitals to the uttermost, so that it was no longer a question of the right patient in the right bed, but almost of any patient in any bed. Last year there was no difficulty. Abortions come in steadily, eight, nine or ten a day, though there is a perceptible rise over these last three years. Applications for unbooked maternity cases show a new and very ugly feature, for they are now about

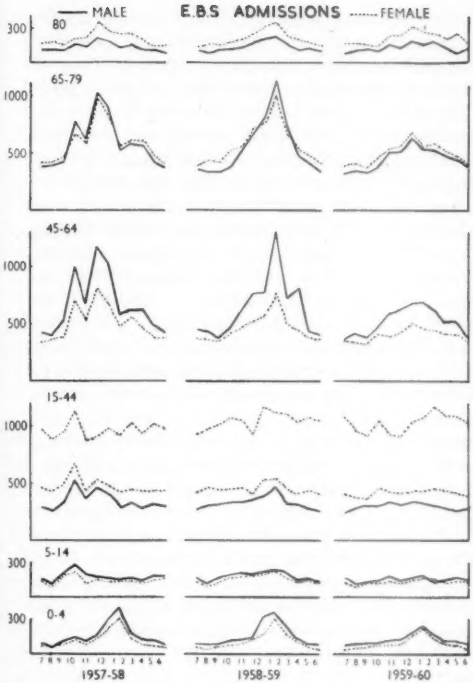

Fig 2 *Emergency Bed Service admissions by age groups*

three times as numerous as they were three years ago. The reasons are obvious, and the remedy is obvious, but of this I have written elsewhere (1959).

Fig 2 presents these figures in another way. Here the admissions, excluding infectious fevers, for the same three years are broken down into age groups, and some curious facts emerge. Why is E.B.S. invariably asked to arrange admission for more male infants than female? Why do boys still predominate at ages from 5 to 14? Naturally, in the child-bearing period of life, women are more frequently admitted than men, but even if from the upper dotted line all abortions and obstetric cases are subtracted we still find women admitted more frequently than men. In the next age group, 45 to 64, there is a clear reversal, and men outnumber women, particularly during epidemics. At 65 to 79, the number of male admissions falls below the female, except, again, at times of epidemic stress, and in the oldest age group women predominate throughout.

There are times when it is a matter of great difficulty to get the right patient into the right bed, or indeed into any bed at all. I wish that there was a better feeling and a greater sympathy, between hospitals and general practitioners. We are all desperately tired on occasion, whether we work outside or inside a hospital. That is when mistakes are made, and patients are needlessly sent in or unthinkingly refused. Just a little more mutual confidence, just a little more understanding between the two worlds, would make a vast difference to the problem of getting the right patient into the right bed.

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Mr V J Downie (*Barnet*)

This paper examines the conventional arrangements by which a patient is allotted a bed in a general surgical ward, and gives an account of arrangements which have been in operation at Barnet General Hospital for the last two years.

One of the treasured relics of a certain hospital in the Midlands is a one-time regulation forbidding more than 2 patients to occupy the same bed at the same time, and an injunction to the effect that should one of the incumbents die, his body ought to be removed as soon as possible. Of recent years we have got into the habit of giving each patient a bed of his own. Segregation of the sexes is also an accepted principle. On very rare occasions this restrictive convention is circumvented by the private enterprise of the patients themselves. The hospital population is further divided, on the basis of age, into three groups: (*a*) Children, (*b*) the aged, and (*c*) the rest. The last two have often to be mixed, owing to the shortage of geriatric beds or the specialist treatment required. Childhood stops, from an administrative angle, at the age of 12, at a safe enough distance from puberty to allow the sexes to be mixed. After this, by recent decree, a child is deemed to have criminal responsibility, and to be a fit associate for his elders and betters in the adult wards. There is no separate accommodation for adolescents, and we do not seem disturbed by the possible effects on sensitive adolescent minds of their abrupt introduction to the seamy side of life in a hospital ward. Pain, death, incoherence, obscenity, and the physical ravage of disease, are grim companions for a teenage child. A patient entering the general surgical wards of a hospital is allotted a bed on these two criteria, age and sex, plus one other—the identity of his surgeon. In the case of an emergency, the surgeon's name is a product of the provisional diagnosis and the duty rota and no other considerations are taken into account.

This paper began with the erstwhile premise that a patient has a right to only half a bed. It will continue with the postulate that a surgical patient requires at least three, and often four beds. Anæsthetists were the first to recognize that one bed is not enough. Modern anæsthetics are wondrous affairs, but for a time they may so dim the

flame of life that if it is not watched, and sometimes fanned, it may go out. A flame is kept alive by oxygen, and it was for lack of this that patients died—in hospital corridors, in lifts, and in dark corners of a sleeping ward. Anæsthetists now rightly demand that every operating theatre shall have an adjacent recovery ward, well lit, adequately equipped, and with an experienced staff, where patients may remain under skilled supervision until the effects of the anæsthetic drugs have worn off. This may be a few minutes, or several hours. In the recovery ward the patient is unaware of his surroundings, and unaware of his 'second bed', but for the remainder of his stay in hospital he is acutely conscious of his environment. Unfortunately he is not likely to share our detached appraisal of the therapeutic paraphernalia which encumber some of his neighbours. 'Emergency Ward 10' has gone a long way in conditioning the public mind to the benefits which accrue from a hypodermic injection, but it is reticent about the duodenal tube, half-hearted in its portrayal of the drip transfusion, and justifiably squeamish in its attitude to the vomit bowl, the sputum mug, and the indwelling catheter.

The newcomer to a surgical ward is understandably curious about the well-being of those fellow customers who have had his 'own' operation, and a man with a grumbling appendix may be forgiven a twinge of misgiving when he finds out that the rather ill-looking appendix case in the next bed has just been reopened for intestinal obstruction. We can sympathize, too, with the candidate for gastrectomy who discovers that the dying man on the other side of the ward had a 'stomach ulcer' removed a year ago. It would be wrong to tell him if we ever thought about it, that the term 'ulcer' can be a kindly euphemism for cancer. If investigations prolong our patient's role of spectator, his stay may be enlivened by the excitements of a burst abdomen, or the more sombre drama of a massive pulmonary embolism. Small wonder that patients in a general ward undergo a period of intense anxiety before an operation, and greater wonder that we have permitted for so long this trial by ordeal.

At Barnet General Hospital the traditional method of allocating beds to individual surgeons has been abandoned, and the general surgical block is divided into two components, acute wards and routine wards. Patients for elective operation, or for observation and investigation, are admitted to the routine wards, whence, in due course, most of them go to the operating theatre. The acute wards receive patients only from the theatre, and only after an appropriate period of observation in the recovery ward which forms part of the theatre suite. Emergency admissions for immediate operation go direct to the theatre from the casualty department. Post-operatively, patients are retained in the acute ward until their recovery is assured, when they either go home or return to the routine wards. The dying are generally nursed in the side rooms of both acute and routine wards, but these rooms are not used exclusively for this purpose, and there is no suggestion of a 'death block'. By this system no patient encounters the distress of others until such time as it is outweighed by his own travail. During the waiting period before operation he enjoys relative tranquillity, and the company of others who are making an uneventful recovery. His nights are undisturbed by emergency admissions or by the colourful therapy which a modern hospital can bring to bear upon the gravely ill. The limited resources in trained nursing staff can be deployed to the best advantage, and to some extent, concentrated on the acute wards. It would be idle to pretend that there are no disadvantages in this arrangement. Some patients – not many – complain of the transfers from ward to ward. Each surgical team loses any proprietorial rights it may have cherished over a particular ward, and the nursing staff have to learn the differing techniques and routines of individual surgeons. These disadvantages were anticipated before the experiment started, but they have not prejudiced its success.

The recovery ward is the province of the anæsthetists, but it may well prove to be the appropriate place for the treatment of certain patients who are customarily admitted to the medical wards. In this group are those suffering from barbiturate poisoning, status epilepticus and status asthmaticus – indeed, any case requiring intermittent positive pressure respiration, or in which the physicians may wish to draw on the special experience of anæsthetists in the field of respiratory physiology.

In private life the bed can look just right . . . or devastatingly wrong. More than any other item of furniture it reflects the personality and habits of its owner. Hospital beds are afflicted by a uniformity of design and decor, and it is pleasing to find that amongst their serried impersonal ranks, some beds can be righter than others.

Dr C Allan Birch (*Enfield*)

The right bed for any patient is the bed in which he can get whatever medical and nursing care is necessary for him. This is obvious enough but occasionally these requirements are not met. This is because the machinery which gets patients into hospital is satisfied once a bed is found. Whether it is the right bed or not is another matter. The right bed must be the one which has the right kind of doctor attached to it. It is sad to see a patient, as I have done, moribund from hæmatemesis in a

Cottage Hospital bed, found for him by the Emergency Bed Service, as a case of gastric ulcer. Practitioners have complained about being kept at the end of a telephone when seeking a bed and also of detailed cross examination by the houseman when he answers it. It is exasperating to have one's clinical judgment called into question by a pre-registration house officer who, when asked to find a bed for a patient comatose from an intracranial vascular accident asks, 'have you tested the urine to exclude diabetic coma?'

Happenings such as these caused the Enfield Group Hospital Management Committee, in November 1957, to set up a Group Admissions office. This office is staffed by one administrative officer and one clerk. It deals with about 1,000 admissions and 200 day cases each month into about 1,000 beds of five hospitals. A bed board showing the bed state in each hospital is brought up to date each morning and then kept correct throughout the day. The office also controls all waiting lists and is able to provide useful statistical information very easily. The appointment of a Group Admissions Officer has brought about many improvements such as a quicker reply to requests for admission from General Practitioners and the E.B.S., better bed occupancy, quicker turnover and a reduction in waiting list. The main theme of my remarks is therefore that the right bed for any patient is the bed in which he can get the particular treatment he needs, and that in finding such a bed, rather than any bed, an Admissions Office is a very great help.

A notice, which I saw in an American Hospital, reminds us that we should aim to provide the right bed with hotel type service. The first sentence reads 'Hotels have accumulated fortunes by astutely commercializing the Biblical injunction "a soft answer turneth away wrath". Hospitals have not yet learned this lesson'. I asked one of my ward sisters which bed she thought was the right one for any patient, and she said 'his own bed at home'. I think the significance of this remark is that at home there would be no ward sister to make the patient stay in bed. Richard Asher in his inimitable way has emphasized how any bed may be the wrong bed for the patient who should be up on his feet. He would put beds and graves in the same category and re-write hymn No. 33 in *Hymns Ancient and Modern*

'Teach me to live that I may dread,
The grave as little as my bed',

and replace it by

'Teach us to live that we may dread,
Unnecessary time in bed,
Get people up and we may save
Our patients from an early grave'.

The poet Ovid wrote

'Deprived of rest all prematurely die,
'Tis this alone that doth our strength supply',

but I do not think that by rest this poet meant necessarily rest in bed.

Cottage hospital beds: My own feeling about these is that, while they are very nice for the straightforward case needing mainly nursing care, they are inadequate when the straightforward case becomes complicated as it often does. Many cottage hospitals have no houseman and the patient's general practitioner may be elsewhere when wanted. Suggestions that cottage hospital beds should be used differently make practitioners fear that they will lose these beds and I favour the setting up of General Practitioner Units within general hospitals. I feel that patients would then be more sure of prompt attention when emergencies arise, and I think the doctors would enjoy working in a busier place.

Casualty beds: The provision of a few beds for the use of the Casualty Officer, and into which he can admit patients for a short time for observation will save admitting patients to the main ward.

More than one patient in a bed: When there are two patients in one bed you will all agree that one of the patients is in the wrong bed. I don't suppose many of us have seen a hospital with two patients in one bed, but I saw this not long ago in a country far away from here. Unfortunately, I did not do what I should have done and that is to take a photograph at the time, and I would like to advise all doctors who travel and see things of medical interest, to make pictures of them at the time. My request for photographs from the doctor at the hospital has been refused for political reasons. However, as this interesting picture is not available, I will read you a short extract from the diary of a surgeon in the year 1751, by John Knyveton, which shows that two hundred years ago it was usual to have several patients in a bed. Describing his experiences as a student he says 'The wards at first sight rather curious, the beds of moderate width, and containing not more than three to four patients, but these placed the feet of one to the head of another, so that each received not the tainted effluvium of their respective complaints. In the infants' wards there were, of course, any from six to eight in one bed. Pregnant women have their own ward to which they are taken when the pains seize them, but from the press those in the earlier stages are frequently put to lie with those about to die, so that comfort is had by both'.

Combined medical and surgical beds: For some conditions such as acute gastro-intestinal hæmorrhage it is probably an advantage to have beds for patients having medical and surgical treatment in the same ward. When this happens the

operation comes to be properly regarded as merely a rather specialized piece of therapeutics.

The medical patient in a surgical bed: A surgical bed while it may be necessary for the surgical condition, e.g. a fracture, may not be the right bed from which to treat a co-existing medical condition. It is not unknown for pernicious anæmia and diabetes to be temporarily neglected in a surgical ward. A more serious mishap arose a few years ago when artificial pneumothorax was the treatment for pulmonary tuberculosis. A patient with an artificial pneumothorax was kept in a surgical ward for some weeks and the refill was not given. As a result the lung re-expanded and a satisfactory pneumothorax could not be re-induced.

Position of the bed: I have found that when small rooms are used, many patients prefer a bed in the corner of the room rather than between two other beds. For some patients the right bed must be on the ground floor. Only a few days ago a patient of mine was caught climbing through the window and had he been upstairs disaster might have resulted.

Beds for smoking: Most management committees have not yet taken the question of smoking in hospitals very seriously, and it is not uncommon to see a patient smoking in bed next to one who has respiratory disease. If a room could be provided, as in some Scandinavian hospitals, to which patients could walk, and into which beds could be easily wheeled, then this would save some irritation of the other patients. The smoking room should not have a cigarette selling machine in it.

Meeting January 18 1961

Discussion on Vertigo

Dr J A Currie (*Reading*)

I thought that as a general practitioner I could most usefully summarize our present knowledge of the disease commonly called 'epidemic vertigo' and report on some recent observations. The condition was first described, so far as I know, by a Doctor Falconer in 1803 (*see* Falconer 1852), who in reporting an epidemic which he thought to be influenza but which clearly was not, described cases which can best be summarized by the following quotation:

'Vertigo and that to a considerable degree, was in some persons the first sign of the disease and in several instances, very alarming and distressful. I saw a lady afflicted to such a degree as not to be able to raise her head from the pillow without losing all sense, and to whom all objects appeared thrice multiplied.' Next, comes Gerlier (1887). His was a very rural practice, and if you read his delightful paper, you will find yourself walking with him through Swiss villages into the fields among the vines, where he noticed that the mildew appeared at the same time as this epidemic and into a cowbyre where the afflicted cowman fell off his stool while milking, landing up under the cow. At least that is what Gerlier wrote. His cases do not however, conform very precisely to the usual picture. His 6 patients, shepherds, cowmen and workers in vineyards, usually got their symptoms in the afternoons rather than the morning. The cowman could manage the morning milking all right, but when it came to the afternoon he would milk say, three cows, then have to stop as he would feel giddy and lose the power in his hands and fingers. He calls this illness 'paralysing vertigo'.

Typical attacks started with a severe pain in the neck, accompanied by vertigo; ptosis would follow and the head would be bowed. 'Paralysis of the extensors' was how Gerlier put it. Peasants driving carts would have to hold their eyelids open to see the way. The attack always ceased when the patient lay down, but this few could afford to do. In searching for a cause, and he did so most carefully, according to the facilities then available, he wondered whether fatigue could be involved and when he found that the harvesters were working seventeen hours a day, he thought he might be on the right track until he remembered the cowman who was doing little more than his usual work.

In 1925 Poston discussed the association of vertigo with encephalitis lethargica, which was present in acute epidemic form from 1915–1922.

In 1936 Miller & Raven at Ramsgate, where one of them seems to have been Medical Officer to a large boarding school for girls, described an epidemic of nausea, vomiting and giddiness, which was not further defined. They concentrated more on the gastro-intestinal symptoms of this epidemic and sought vainly for food contamination. A Dr Storr in Cornwall, quite clearly had a short-lived attack of nausea, vomiting and vertigo himself at that time.

In 1933 Leyton reported attending a colleague aged 40; 3 of the staff in his house were affected, as were his secretary and her husband, and finally himself also.

In 1949 Dr Walford of Essex reported 4 cases which he thought might be epidemic but thanks to careful recording and follow-up, he was able to report last May (personal communication) that 2

had subsequently developed disseminated sclerosis, one had developed a full Ménière's syndrome and one had further attacks of vertigo over the years.

In late 1952 the following occurred. The *Lancet* produced an annotation under the title 'An Unusual Epidemic' stating that one doctor in Hampstead had seen 6 cases between January 11 and 28, but had also diagnosed in retrospect 3 cases seen in March, April and October 1951. The annotation went on to say that 'we heard of 3 cases referred to a neurologist during the last few months and a single case seen by another general practitioner'. The annotation produced a marked reaction. Recent cases were reported by a number of general practitioners from widely spread areas, and by two neurologists, so it might be thought that an epidemic was in progress. I myself was mildly afflicted – and considerably worried – until Dr G H R Curnock, one of my partners, drew my attention to the *Lancet* annotation and I saw further cases in my own practice in rapid succession; one of my partners also reporting a further case.

At the same time, two housemen at the Radcliffe Infirmary fell on the floor. In the course of a few weeks, reports from Britain ceased to come in but a French doctor in Normandy also reported seeing a number of cases about the same time as those seen in England. Raffle (1954) reported seeing a series of cases from South Shields, Yuille (1954) reported 7 cases in one month and Leishman (1955) 6 cases accompanied by diplopia in the Rotherham area.

Now we come to a much more convincing epidemic.

In 1955 Newell-Price (1956), who was Medical Officer to an Army School of Physical Training, saw 33 cases between mid-November and mid-December. Weakness and severe headache were common; the headache was felt behind the eyes and there was true vertigo in two-thirds of the patients, but only one complained of diplopia and that was transient. A constant severe lumbar backache on the second or third day, not uncommon in ordinary influenza, was also noticed in 10 cases. Nystagmus was very common but Romberg's sign was always negative. He used a more severe test, asking the patients to stand on one leg with their eyes shut and this brought out the unsteadiness. Illness lasted two to nineteen days and no relapses were reported. He thought that the incubation period was two to four days and, based on the slow spread of infection through any one hut, he thought that the infectivity was low. He used antihistamine drugs but did not think that they altered the course of the disease.

In 1955 Marshall in Kent saw 6 cases, 1 of whom had a coronary thrombosis while bicycling home, and from which he died. Serial sections were taken through his inner ear, all of which were negative. Marshall suggested hopefully, and probably very wisely, that 'next time it would be well to look at the mid-brain'.

The latest observations started in this way. I saw 3 severe cases consecutively in March and April 1960, and reported this to Dr G I Watson of Peaslake who promptly sent out a questionnaire to members of the College of General Practitioners. As this was based to some extent on my own cases, I must outline some details. My report was as follows:

March 6 1960 – a housewife aged 41 had a sudden onset of acute vertigo, so severe that I transferred her to hospital next day. A diagnosis of acute labyrinthitis was made and she was not discharged for four weeks. **March 27** – a man aged 54 similarly affected.

April 24 – by now I had seen a further 5 cases; 1 of my 6 partners had seen 2 more.

Symptoms: Giddiness on rising or turning in bed 'when the room goes round as if I had had too much to drink, Doctor'. There was no vomiting.

Signs: On attempting to elicit nystagmus the more severe cases recoil, covering their faces; they reel in their gait but Romberg's sign is not present. I have found walking heel to toe a more useful test. There are no associated auditory symptoms, or signs; blood pressure is normal and only one patient was febrile.

The doctors were asked as follows:

(1) 'Have you encountered similar cases of acute vertigo during the last six months?'

(2) 'If you see any patients affected in the near future, will you please report details including age, sex, date of onset, associated diseases and brief clinical notes.'

Although not asked for, nil returns were sent in by many receiving the questionnaire, which was most helpful. What Dr Watson did was to alert some of the keener clinical observers, over quite a wide area, ranging down the Thames valley from Lechlade to London, and the counties of Middlesex, Bedfordshire, Hertfordshire and Essex.

108 doctors reported out of a possible 387, and 32 reported between them on 53 cases. I had to exclude some reports before analysis, as the necessary details were lacking, so that 48 cases were finally studied. The incidence was as follows:

Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June
2	2	3	4	3	7	21	3	3

Geographical distribution: If the cases are arranged in the order of date of onset, there is no obvious pattern of distribution. Cases occurred all over the area reported on, during the peak period, mid-March to the end of April.

Age: The age groups 30 to 60 were most affected, but the range fell between 4 and 75. The diagnosis in the first case was confirmed by Dr White Franklin, Consulting Pædiatrician at St. Bartholomew's Hospital. It will be interesting to know the subsequent history of the man of 75.

Other diseases prevalent: Diarrhœa and vomiting – particularly vomiting – occasionally due to Sonne dysentery, was not infrequent during the peak period. The vomiting did not precede the vertigo. But others reported only a background of chicken-pox and measles, and in some cases no other disease was prevalent.

The signs and symptoms pattern was set by the questionnaire, and no cases of diplopia were reported, but this was not specifically asked for and could have been missed.

Progress: Recovery rates were often not reported, but the average of those giving the necessary details worked out to between three and four weeks. Some recovered much more quickly. The boy aged 4 recovered in five days. We have, of course, no long-term follow-up in these cases at present, though one cautious doctor held on to his reports for six months before sending them, to be sure that his diagnoses were sound and not vitiated by further untoward developments.

Treatment: Some gave antihistamines and/or barbiturates; an antibiotic was also given by a few. Others gave none. There was no evidence that the treatment given was of any value.

Infectivity: No immediate contacts were reported to have contracted the disease. While this was not specifically asked for, the care and thought put into their reports by some, make it certain that this would have been reported, if it had occurred.

In summary, this may have been a true mild epidemic, probably associated with a gastro-enteritis, which would not have been uncovered if the machinery of the epidemiological observation unit of the College of General Practitioners had not been available. It has reminded, and I hope refreshed, general practitioners, who may well be alarmed when encountering a severe case with its rather dramatic and puzzling picture of the occurrence of epidemic vertigo.

There are some however, and I must thank Dr P A Walford for emphasizing this, who may think that this so-called epidemic was an artifact. Their arguments run as follows:

It is well known that sporadic cases of acute labyrinthitis occur from time to time. In this instance, Currie who was already alert to the condition because it had frightened him, happened to see 3 cases in rapid succession – a not uncommon occurrence in medicine. A large number of keen observers now wearing as it were, Currie's spectacles, thanks to a heavily slanted questionnaire, 'swung into action'. The usual burst of short-lived activity followed. Enthusiasm was set up by the questionnaire. People easily recollected cases that seemed to fulfil the criteria, the finer details having been blurred over by time. They hurried to report their cases, sent off their replies almost at once, and then most of them waited. Does it surprise you that a sharp rise of cases occurred in April? We must not forget that the questionnaire reached them at the end of that month.

I think these are valid criticisms and must be met.

First, the sporadic cases. Are these cases truly sporadic or is it a disease of low infectivity, always prevalent, that now and then emerges into the open? A similar project on herpes zoster but slightly differently organized would be interesting.

To see 3 cases of a fairly unusual complaint in rapid succession is odd enough. To see 5 with the partner seeing 2 more is, I would have thought, highly significant. Many of the reports received, giving careful clinical details, are impressive and do not read like the work of enthusiastic 'journallists'. The date-spread would seem to be significant. The cases fall neatly round early April and the dates were arrived at quite independently one from another.

That epidemic vertigo occurs there can be no doubt. No reader of the Danish report (Pedersen 1959) could query that, and we had here, a mild epidemic in which the resistance of the population was far greater than in some other epidemics described. Alternatively, we are faced with a new factor to confuse us – 'the epidemic observation unit effect'.

I have many to thank, particularly Drs Walford and Watson, all those who so kindly reported, Mr T F Howarth, the Librarian of the B.M.A. and Mr P Wade, the Librarian of this society – without whom I should never have met Dr Gerlier or his cowman.

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Mr C Gill-Carey (*London*)

As vertigo is such a wide subject, I propose to confine myself to the diagnosis and immediate treatment of a patient with vertigo.

From a diagnostic point of view, vertigo falls into four main groups: (1) The syndrome described by Prosper Ménière, and which is rightly

known as Ménière's disease. (2) Vertigo associated with middle ear disease or injury. (3) A group of virus diseases which affect the labyrinth, such as mumps or herpes. Others may occur in epidemics. (4) Certain drugs have a selective toxic action on the vestibular portion of the labyrinth; of these the only one now commonly in use is streptomycin.

By far the commonest cause of vertigo is disease of the internal ear. This is contrary to the general view held a hundred years ago, when all cases of vertigo were regarded as a cerebral catastrophe. Cawthorne (1957), reviewing 2,500 cases recently, reported that 80% of all cases of vertigo were of aural origin, and of these 80%, more than half were due to Ménière's disease.

I must pay tribute to Dr Prosper Ménière, himself a general practitioner, who, exactly a hundred years ago, in 1861, by noting the connexion of deafness in association with vertigo, was the first, and has remained the greatest, contributor in this field. So accurate were his observations, that his descriptions of the varying types of vertigo are still quoted to-day. Before retailing these, however, I must recall briefly the anatomy and physiology of the internal ear. This will underline the fact that the pattern of attacks may vary.

There are five end-organs in each internal ear and their function is to maintain the position of the head and body in space, at rest, and in motion. Further to complicate the issue, the ten end-organs are interdependent, so that loss of function on one side is proclaimed by the symptoms of over-activity on the other side. Whether this produces a violent attack, or whether it is virtually symptomless, and only productive of vertigo with certain movements or positions of the head, depends not only upon the extent of the damage, but upon the speed with which the damage occurs.

Separate end-arteries, branches of the internal auditory artery, supply the cochlea and saccule, and two or three further branches the remainder of the labyrinth. There are no anastomoses between any of these vessels. This vascular supply is the key to the selective nature of the attacks of vertigo in Ménière's disease. Here it is easy to see that a single portion of the labyrinth may be picked out for damage, the rest of the labyrinth being left intact, or the whole of the internal ear may be affected, depending on the position of the lesion in the vascular tree.

The current popular theory of Ménière's disease, and one to which I personally subscribe, is that in the main this syndrome must be due to anoxia of the internal ear. Whether the vascular disease produces thrombosis, embolism, or spasm, mild and temporary, or severe and prolonged, with consequent permanent damage, is only a matter of degree, but the theory fits the many clinical pictures of vertigo.

Ménière described four types of vertigo, and these descriptions apply to all cases of peripheral vertigo, whatever their ætiology.

(1) The true rotatory vertigo, which comes on without warning, when the room appears to be whirling round. These attacks last from two to twenty-four hours. There is no loss of consciousness and there is no weakness or paralysis.

(2) A feeling of unsteadiness, and a tendency to bump into objects sideways.

(3) An up and down movement, or a side to side motion, as if in a ship on a stormy sea.

(4) The most dramatic type: the patient is thrown suddenly and violently to the ground, and lies there vomiting.

Ménière also described a condition which existed between attacks, in which certain movements of the head may produce an attack of vertigo. I should mention that, together with any of the foregoing symptoms, the patient frequently complains of a heavy feeling in the head, and often a feeling of one-sidedness, as though one side of the head were filled with putty.

How then shall we set about the task of differential diagnosis? In all cases, general examination of the patient directed towards the exclusion of disease of the central nervous system, should precede examination of the ear. In this I would include the test for corneal sensitivity, Romberg test and an examination of the optic discs.

In these cases the history is of great importance, as even in patients with loss of consciousness, this does not preclude them from describing accurately the events which led up to their attack. In this way if differs from forms of epilepsy, where patients have a vertiginous aura.

The simple case of Ménière's disease presents no difficulty, as in addition to the vertigo, there is always deafness in some degree, and the caloric test, when performed, is usually abnormal. Unlike the audiogram, the caloric test is not a precise measurement of degree of function in the vestibule, but it shows whether or not there is abnormality of function.

A real pointer to diagnosis is the nature of the deafness in Ménière's disease. This is a true end-organ deafness, and as such has definite characteristics. These include:

(1) Recruitment of loudness. This can only be truly demonstrated by audiometric testing, but roughly it means that the loud sound is heard as well, or even better, in the affected ear, whilst the soft sound is missing, or even absent, in the affected ear.

(2) Excessive sensitivity to loud sounds.

(3) Patients hear sounds at different pitches in

each ear. With the tuning fork they usually hear a higher pitch in the affected ear.

(4) Distortion of sound is frequently bitterly complained of.

(5) The deafness fluctuates, and is worse during an attack.

From a summary of these symptoms of deafness, it will be seen how difficult it is to help the really deaf sufferer of Ménière's disease with a hearing aid.

The real difficulty in diagnosis is with the early cases of Ménière's disease, in which there may be no loss of hearing, or so small a loss that it can be detected only by the audiogram. During the acute attack, anti-histamine derivatives have been found more effective than either barbiturates or hyoscine (Jongkees 1960). Dramamine, dimenhydrinate, 50 mg given intramuscularly, and repeated in one or two hours, has been found to control the symptoms. Apart from this, with the doubtful case of Ménière's disease, there is nothing to be done. Inevitably, as the disease progresses and the damage to the internal ear becomes permanent, the deafness, in addition to the vertigo, shows itself.

In my second group of cases of vertigo, there is associated middle ear disease. Difficulties in diagnosis are likely to occur only when the lesion in the drum is difficult to see, and where the hearing is good, as for example a small attic perforation filled with a mass of cholesteatoma. Here, two simple tests should be applied.

(1) *The fistula test:* When this sign is positive, pressure on the tragus on the affected side produces giddiness, and indicates a fistula into the semicircular canal. When this sign is positive, and in the presence of middle ear suppuration, only surgery will help. Antibiotics should only be used as a cover for the surgery, and not as a curative measure.

(2) *Positional vertigo:* This test can be found to be positive in cases with or without middle ear disease, but it is a useful test to perform, and very simple. The patient is placed supine with the head slightly lower than the body, and the head is then rotated to the right, and then to the left. If giddiness is produced, it will be when the head is turned to the side of the lesion, and it is then said to be positive. This test is fatigable, and can therefore be distinguished from positional vertigo, of central origin, which remains constant.

In my third group, vertigo is due to a virus infection. Here the diagnosis is difficult, and must depend upon signs of associated disease. Herpes on the pinna and drum, and inside the mouth, must be searched for. There may be herpes on the face, following the course of one or more of the branches of the V cranial nerve, or there may be weakness or paralysis of the VII or facial nerve. The difficulty here is that there may be no associated damage to other cranial nerves, indeed the virus may only have affected the vestibular branch of the VIII nerve, so there may be no associated deafness. The caloric test will, however, be abnormal, and is thus a pointer to diagnosis.

The fourth and last group consists of those cases of vertigo where the inner ear has been damaged during the course of treatment with streptomycin. This is the only antibiotic now in current use which has this selective toxic action on the VIII cranial nerve, and in particular on the vestibular branch. If the dosage is heavy and prolonged, the cochlea will also become affected, with consequent deafness and if the patient has inefficient renal function, these changes are liable to develop soon and on small dosage.

When giddiness or deafness is complained of, the drug must be stopped immediately, to prevent further damage. In a proportion of cases the damage is not permanent, and almost normal function is re-established. In some cases, however, the damage is too extensive to be reversible.

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Dr Denis Williams (*London*)

The neurologist sees many patients with vertigo, some presenting with this complaint, and others having it as part of a more extensive syndrome. He is often surprised, when he refers the patient to an otologist, to find that cochlear and vestibular mechanisms in the ears seem to be normal. When this happens, he may have difficulty in finding a cause for the symptom.

Though strictly speaking vertigo should mean a sense of turning round, clinically it includes any sense of imbalance, whether rotatory or not. Some patients complain that they feel that they are being pushed to either side, forwards or backwards, and others that they have a sense of swaying as if they had just stepped off a ship. In some, the sense of disequilibrium is so mild as to be bewildering to the patient and to his advisors, and is thought to be the result of neurosis. In some of these people with mild disorders of equilibrium the condition may be continuous rather than episodic, as in the classical examples of aural vertigo.

If the examiner is satisfied that the patient has true vertigo in this sense, rather than simply giddiness or faintness, it is then certain there must be disorder of the labyrinthine mechanism. Vertigo cannot arise from any other cause. Some

people with ataxia have difficulty in deciding whether they feel giddy in their head, or unsteady in the legs, but if the unsteadiness of the legs is the result of vestibular disturbance, the patient should also be able to describe a sense of imbalance in the head, if asked about it directly.

Vertigo may have a peripheral or a central cause, and I shall confine myself to consideration of the central causes and their effects.

The differential diagnosis of vertigo of central origin from that of aural origin may be difficult. In each case the vertigo may be intermittent, induced by movement or change in posture, and in each, the patient's subjective symptoms are the same. There is no way, without quantitative labyrinthine testing, to establish the distinction, other than the recognition of associated symptoms. The patient with aural vertigo or Ménière's disease will have tinnitus and probably deafness, and other patients with vertigo of peripheral origin may have a story of previous ear infection or injury. On the other hand people with central vertigo may experience other neural disturbances in the attack, such as diplopia, teicopsia, or other disturbances of vision.

Central vertigo: Vertigo of central origin is met particularly in older patients, particularly above the age of 50, and it is likely to be induced by change in posture, rising from the recumbent position, and by extreme neck movement. It happens, for instance, after backing a car, or after extending the neck for some time. In younger people it may complicate neurological disease such as disseminated sclerosis, tumours of the brain-stem, particularly acoustic neuromas, or head injury. Here there is little relationship to the patient's age. It is important to appreciate that after quite a short course the VIII nerve enters the lateral part of the pons, and the vestibular nuclei are placed far laterally in the middle cerebellar peduncle with extensive connexions laterally to the roof nuclei in the cerebellum, downwards in the afferents from the postural muscles and upwards to the vestibular cortex. There is consequently plenty of opportunity for damage to the nucleus or its connexions.

The causes of central vertigo: We need not here consider disturbances of equilibrium complicating gross neurological disease. We are considering the complaint of vertigo as such. All of us are aware of the ageing patient who comes complaining of periods of giddiness for which no adequate cause can be found, and it is these people whom I want to consider particularly. If there is no evident cause in the ear for the giddiness and if there is no associated deafness, it is wise to enquire most carefully for visual changes, either blurring of vision or frank diplopia, or the appearance of visual defects. These may take the form of spots, either black, white, dazzling or coloured, or of obscurations of vision. The spots often move about and are described by such words as tadpoles, snowflakes or soapflakes. The attacks of giddiness may be associated with tingling in the face, ataxia, weakness of the legs and sometimes by loss of consciousness. When no cause for the disorder can be found in the ears and when associated neural disturbances of this sort are being experienced it is probable that the cause of the intermittent vertigo is vascular. We are now learning, through the use of arteriography, that many ageing people have complete occlusion of one of the great vessels supplying the cranium. A carotid or vertebral artery may be occluded. Narrowing or absence of one of these vessels may be the result of a congenital anomaly. Good health is quite possible through the collateral circulation via the circle of Willis, and through other smaller arteries in the face, in the neck and in the orbit. In later life, as a result of arteriosclerosis, this collateral supply may be inadequate and intermittent neural symptoms will develop. Often the subjects of attacks of this sort will be found to have a blood pressure which is either normal for their age or low for it. Although blood pressure may be normal for the age group, it is inadequate for that particular patient's needs.

In people who seem to have central vertigo it is therefore well to search for evidence of arterial degeneration, fluctuation in blood pressure, anæmia and recent dehydration, through diarrhœa for example. It is also wise to enquire carefully about the effect of neck movement, and to look for cervical arthritis which may impede the flow of blood through the vertebral arteries.

Blood flow: Arteriography is now showing us that many intermittent disturbances in the elderly are not the result of thrombosis of vessels, as used to be thought, but of transient diminution in the rate of flow of blood through them. This rate of blood flow, though dependent upon the level of the blood pressure, is affected by the lumen and length of the vessel, the peripheral resistance and the viscosity of the blood. Flow varies from moment to moment, it is affected by obstruction remote from the site of its effects and it decreases along the length of a narrowing vessel. It follows that the vestibular nuclei far out in the pons are especially vulnerable to reduction in blood flow, particularly because they are supplied by the tenuous long lateral branches of the basilar artery. The basilar artery is particularly vulnerable, for its parent vessels, the vertebrals, are also long, subject to congenital anomaly, damaged by neck movement and osteophyte formation and particularly liable to atherosclerosis. Vertigo is by far the most common symptom of insufficiency of basilar blood flow. This disorder is comparatively

common. I found 66 examples in a consecutive series of a thousand patients. As the basilar-vertebral system supplies the whole of the brain-stem and ultimately the occipital and temporal lobes of the brain through the posterior cerebral arteries, the effects of ischæmia are very various. The exact pattern of symptoms which the patient experiences depends not only upon the site and degree of the occlusion of vessel, but also upon the capacity for collateral flow through the posterior communicating arteries from above. Classically, central vertigo, the result of diminished flow, is associated with visual changes of the sort I have described caused by ischæmia in the posterior cerebral arteries. It can be associated with a number of other symptoms which have been mentioned previously, and will even be accompanied by deafness, for the artery to the middle ear comes from the basilar.

If the varied, intermittent and dynamic nature of these syndromes of deprivation in the elderly is recognized, the management of many examples of vertigo will have a more rational basis than at present.

Treatment: If there is central vertigo the symptom itself can be treated by the use of sedatives of exactly the same kind as are used for vertigo of aural origin. The basic treatment is that of the cause and its details are beyond the range of the present discussion. When vertigo is arterial in origin it is the general rule that the patient's blood pressure is inadequate for his needs at the time of the vertigo. There is now some conflict between general physicians, who want to lower blood pressure to safeguard heart and kidneys, and the neurologist who wants to keep it up to safeguard the central nervous system. In general, hypertensive substances should not be used, but the blood pressure should be raised by attention to details of bodily hygiene, to exercise and to a full diet with gain in weight. Ephedrine 0·03 mg or methylamphetamine 5 mg in the morning and possibly at midday will for a time raise the blood pressure though, as many of the patients are arteriopathic, these drugs may be ineffective. It is most difficult to maintain blood pressure persistently by medical means. The question of the long-term use of anticoagulants is still being debated but in the situation I have described there is an identical state of affairs to that in the heart, where diseased arteries have a collateral supply of blood from their fellows. If there is narrowing of vessels proximal to the circle of Willis it can be argued that anticoagulants, preventing final thrombosis, may be of benefit to the subject, and empirically this seems to be the case. Finally, it is wise to consider the effect of posture and neck movements on the patient, and the use of a foam rubber ruff at night, arrangement of pillows to stop angulation of the neck, and even plastic collars in the daytime may be of great benefit. Of almost as much benefit to the patient as the relief of his symptoms is the recognition of their nature to prevent faulty and misdirected management.

Section of Obstetrics and Gynæcology

President W R Winterton FRCOG

Meeting November 25 1960

Discussion on Infertility

Dr C Lee Buxton (*Yale*)

Anovulation due to Pituitary Failure – Diagnosis and Treatment[1]

Anovulation, either occasionally or consistently, ranks among the most frequent and sometimes the most obscure causes of infertility (Rock *et al.* 1939).

Contrary to the old German dictum 'ohne Ovulation, keine Menstruation', it is possible for cyclic bleeding of reasonable regularity and amount to occur in the absence of ovulation and subsequent progestational activity – a fact which sometimes conceals this ovarian ineptitude.

Therefore available diagnostic procedures must be used in the investigation of the infertility patient to determine as well as possible the quality and quantity of ovarian activity. From a practical point of view the basal body temperature chart and the premenstrual endometrial biopsy are the most useful techniques for this purpose. If these tests consistently disclose absence of progestational activity, a search must be made for the causative factors.

For the purposes of this discussion, the investigation and treatment of anovulation will be considered together with the symptom of amenorrhœa – certainly a more definite symptom but frequently having the same ætiology. The causative factors may be searched for by a process of elimination of the type described in Table 1.

Since this paper is concerned with pituitary failure as a causative factor in anovulation and amenorrhœa, the physiological, congenital and systemic causes will be considered to have been eliminated, leaving hormonal and psychological factors, in which pituitary abnormality may certainly play a part.

Under these circumstances then, we must search for aberrations of function all the way from the cerebral cortex to the endometrium itself. How is this best done? It is sometimes difficult, if not impossible, to separate psychological from hormonal ætiologies because the former usually produces the latter. We are now, in fact, concerned with cerebral cortical→hypothalamic→hypophyseal→ovarian→endometrial relationships.

Table 1
A suggested 'check-off' list for the investigation of the ætiology of amenorrhœa

Cause:	Physiological	Before menarche After menopause Pregnancy Lactation
	Congenital	Absence of one or more genital organs
	Psychological or environmental	
	Pathological	Systemic disease
	Hormonal	Inadequacy of pituitary, thyroid, adrenal or ovary

Harris (1956) is of the opinion that the anterior lobe of the pituitary is a liaison organ between the nervous system, which is affected by stimuli from without, and the endocrine system which produces the response to that affective stimulus. Certainly the portal system between the hypothalamus and the hypophysis presents a very rich vascular bed and must be of significance. Cleghorn (Wittkower & Cleghorn 1954) has made a simplified diagram of this relationship (Fig 1). Probably neocortical control is passed through the hypothalamus and the hypophyseal portal vessels of the pituitary stalk by the transmission of a humoral mediator. In a general way these portal vessels may be described as the anatomical connecting link between the external environment on the one hand and the anterior lobe of the pituitary and its target organs on the other. 'The loss of activity and atrophy of the gonads for instance that follows "denervation" of the anterior pit-

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The human chorionic gonadotrophin used in this study was APL supplied through the courtesy of Ayerst, McKenna and Harrison Ltd. The human pituitary extract was prepared and supplied through the courtesy of Merck & Co.

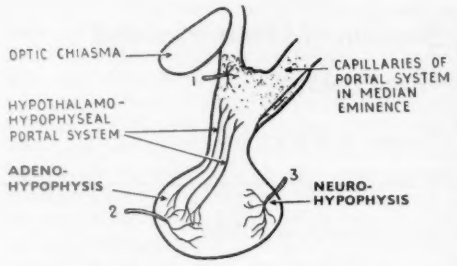

Fig 1 *Diagram of blood supply to the pituitary gland. Arteries numbered* 1, 2, *and* 3 *arise from the internal carotid. No.* 1 *breaks up into a multitude of capillaries in the median eminence. These coalesce into portal venules carrying blood from this region down the pars tuberalis to the pars distalis. There they break up into sinusoids and the blood mingles with that from the direct arterial supply from the carotid. Venous drainage is to the cavernous sinus. The blood supply to the neurohypophysis, except for the median eminence, is separate. Reproduced from Wittkower & Cleghorn (1954) by kind permission*

Fig 2 *X-ray of sella turcica in patient with chromophobe adenoma of the pituitary. Note the erosion of the floor and clinoid processes*

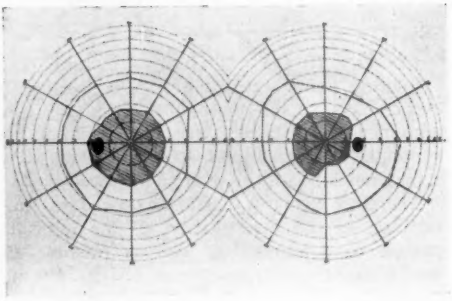

Fig 3 *Visual fields in patient with pituitary tumour. Note unilateral restriction*

Figs 2 *&* 3 *are reproduced from Buxton & Southam* (1958) *by kind permission*

uitary gland may be explained in terms of loss of the effect of the multitudinous stimuli to which the organism is continuously subjected from its surroundings' (Harris 1956).

Therefore in our search for the organ or gland at fault in the anovulatory or amenorrhœic patient whose trouble is thought to be due to psychological or hormonal factors, let us start with the end organ – the endometrium. The condition of the endometrium is easily determined by biopsy. We then assess ovarian activity by the simple process of evaluating a vaginal smear. There are, of course, more accurate methods of measuring œstrogen activity, but, by using the patient as her own test animal as it were, a good approximation of œstrogenic activity may be obtained by observing the amount of cornification of vaginal epithelial cells.

Proceeding to evaluation of the pituitary, we obtain a twenty-four-hour urine specimen for the determination of follicular stimulating hormone (FSH). Although a combined chemical and biological assay this is not a particularly difficult laboratory procedure and is most important in this type of case.

Excessive FSH excretion of 100 m.u.u. (mouse uterine units) or more, accompanied by failure of cornification of vaginal cells is ample evidence of ovarian failure, due either to disease or the primary ovarian failure known as the menopause. Here the hypophysis is secreting large amounts of FSH unchecked by the depressant effect of œstrogen.

Not infrequently however, the type of patient in whom we are presently interested shows evidence not only of ovarian failure but also a zero or very low FSH output, thus indicating failure of the pituitary to stimulate ovarian function. It is under these circumstances that an attempt must be made to differentiate between psychological causes and organic hypothalamic or pituitary disease.

Occasionally in well advanced cases the diagnosis of a pituitary tumour may be made by X-ray (Fig 2) or visual field changes (Fig 3). Such cases may be successfully treated by pituitary irradiation. If, on the other hand these diagnostic tests are apparently normal, the search must be continued.

Rhythmic hypophyseal gonadotrophic activity may be graphically represented as in Fig 4, with the tidal undulations of different gonadotrophic secretions familiar to us all. Very possibly the first evidence of gonadotrophic decline is a decrease in the secretion of FSH, because, in cases of pressure

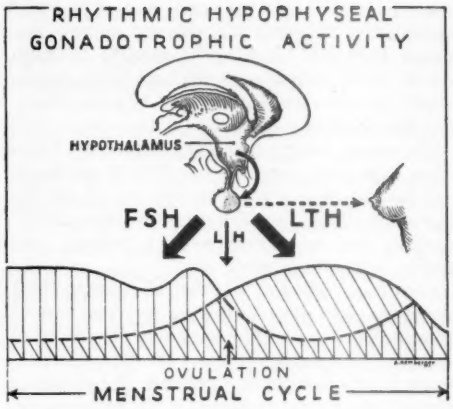

Fig 4 *Theoretical graphic representation of rhythmic gonadotrophic activity and its effect on the secretion of ovarian steroids and on the breast*

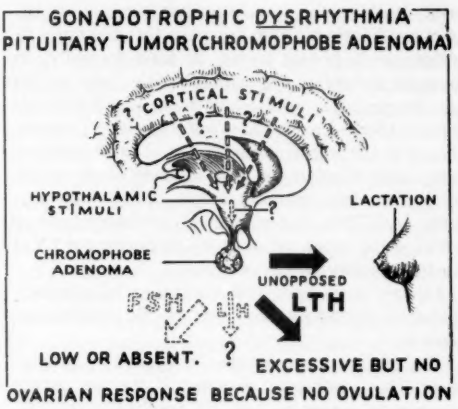

Fig 5 *Graphic representation of theoretical selective decrease in different gonadotrophins as a result of pituitary disease. (Selective because FSH excretion disappears or is greatly diminished yet lactation is frequently stimulated—demonstrating possible uninhibited secretion of Prolactin (LTH). The same apparently selective decrease may occur in hypothalamic disease or in failure of cerebral cortical stimulation*

producing pituitary tumours such as chromophobe adenomas for instance, FSH is no longer excreted but the patient frequently produces colostrum or milk on nipple pressure or may even lactate. A hypothetical idea of why this occurs is represented in Fig 5. Interestingly enough, these symptoms also occur in hypothalamic disease, as has been described occasionally in cases of localized encephalitis (Fig 6). To complicate matters further, amenorrhœa, low or zero FSH excretion and lactation also occurs in psychiatric failure to stimulate hypophyseal activity (Fig 7). This symptom complex, regardless of ætiology, was first described by del Castillo in 1953 (Argonz & del Castillo 1953), and deserves more than passing mention. A surprisingly large number of non-pregnant anovulatory and amenorrhœic patients may be found to produce either colostrum or

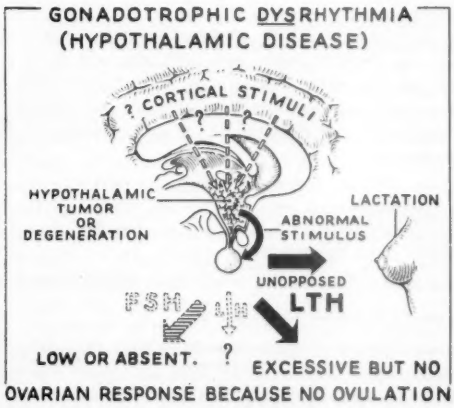

Fig 6 *Possible selective uninhibited secretion of LTH and suppression of FSH in hypothalamic disease. A theoretical concept*

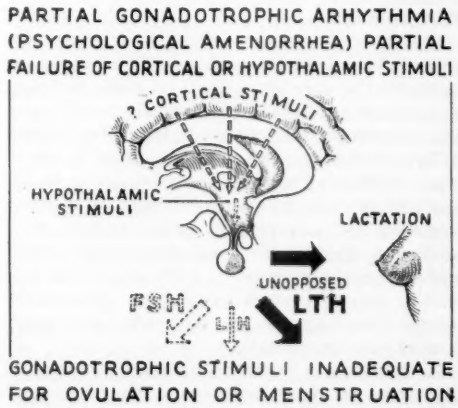

Fig 7 *Possible selective uninhibited secretion of LTH and suppression of FSH in psychological amenorrhœa. A theoretical concept*

milk. With us this condition has become an important diagnostic sign – not in the diagnosis of pregnancy – but in trying, at least partially, to localize glandular abnormality. We have yet to see, for instance, a patient with polycystic ovarian disease (Stein-Leventhal syndrome) who presents this type of breast condition. It is interesting to conjecture whether the pituitary selectively ceases to secrete one gonadotrophin (FSH) and not another (LTH). The answer will probably have to await some more satisfactory technique of LTH assay, possibly immunological.

In any case, once this condition of pituitary failure is identified, what therapeutic possibilities have we?

The pituitary tumour may be treated by irradiation. The psychiatric patient, if we are astute enough to recognize her, by psychotherapy; although many of these must fall into what might be called, for want of a better designation, the idiopathic group. These latter cases until recently have presented an almost hopeless therapeutic problem. Treated over the past twenty years with every type of gonadotrophin that became available, few patients with pituitary inadequacy responded. Chorionic gonadotrophin, pregnant mares serum, pituitary extracts from sheep, cattle and hogs, as well as various 'synergistic' combinations of these were equally disappointing. This may have been at least partially due to a failure to provide species specific gonadotrophin. Considering the latter factor as a possible cause for lack of success, van Wagenen and Simpson (1957), using pituitary extracts from rhesus monkeys, produced multiple ovulations in these animals. Since then Gemzell (Gemzell *et al.* 1958), as well as our clinic, has had similar success in the human with the use of human pituitary extract obtained from autopsy material (Buxton & Herrmann 1960).

Up to the present time 8 amenorrhœic patients have been given a total of 16 courses of injections in our clinic. Two of these patients complained of primary amenorrhœa, one being a case of adrenal cortical hyperplasia. The others suffered from amenorrhœa of from three to seven years duration. Their ages varied from 22 to 33 years. Most of these patients had been extensively treated by us and others by various techniques – uniformly unsuccessful – and all had had investigative studies consisting of FSH and 17-KS excretion assays, vaginal smear and endometrial biopsy interpretation, thyroid studies and basal body temperature charts.

A therapeutic regimen, modelled somewhat after that of van Wagenen and Simpson, consisted of a preliminary trial with human *chorionic* gonadotrophin (HCG) only, administered in amounts of 1,600 units on four successive days. Interestingly enough, one patient ovulated and menstruated following this therapy on two successive occasions, and has continued to menstruate since, even though she had been amenorrhœic for three years previously. She was therefore discarded from the series.

The others, having had no reaction from HCG alone, were then given courses of HCG combined with human *pituitary extract* (HPG), 25 mg for four days. This was followed by anovulatory bleeding on six occasions in 4 patients and ovulatory bleeding twice.

The dosage schedule was then changed to HPG 25 mg for eight days during the last four days of which 1,600 units HCG were added. Evidence of ovulation was present in each of seven cycles produced in this fashion in 4 patients. Subsequently similar results were produced in the patients previously recalcitrant on the first regime.

Culdoscopy was carried out on one patient. Several bleeding points which looked like freshly ruptured follicles were seen on both ovaries, each of which were hyperæmic, enlarged, bluish and cystic. It seemed most important however to obtain, if possible, actual microscopic evidence of this apparent ovarian stimulation. A 38-year-old female with endometriosis requiring operation consented to a pre-operative series of injections and it was therefore possible to observe the results both at laparotomy and later microscopically. The ovaries of this patient were about four times normal size, being distended by hæmorrhagic cysts which, on microscopic examination, proved to be corpora lutea. There were several on each ovary and seemed to be, when judged by the criteria of Corner and others, as much as 24 to 48 hours different in age.

If combined HCG and HPG injections continue, on further trial, to produce ovulation in this fashion its implications in the therapy of the anovulatory and amenorrhœic infertility patient are obvious. Possibly one difficulty will be the production of this material on an adequate scale, especially since neither Gemzell's nor our patients continued to menstruate after cessation of therapy.

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Dr Albert Sharman (*Glasgow*)

Latent or Subclinical Genital Tuberculosis in Female Infertility

The present communication concerns 275 cases of endometrial tuberculosis in 4,817 patients with primary sterility submitted to biopsy or curettage, an incidence of 5·7% during a period of twenty-four years, 1935 to 1958. The incidence in the most recent cases, 1955-1958, is 5·8%, a figure approximating closely to the incidence of the entire series.

The age of the patients in the series ranged from 19 to 43, there being two aged 19 and one aged 43. 67% (184) were between 20 and 30 years of age. In none was pelvic tuberculosis diagnosed or suspected before endometrial biopsy. Almost all were noted as enjoying good health. Radiography of the lungs in 163 cases showed 40 with healed tuberculosis, mostly apical; 3 additional patients showed active pulmonary tuberculosis.

Seven patients with a history of tuberculous abdominal glands or peritonitis are of particular interest. In 4 of them, laparotomy at 16, 17, 22 and 24 years revealed the condition. Two of the remaining patients had been for several months in sanatoria at the age of 14 years, and one of 3 years 5 months was diagnosed at laparotomy at the Royal Hospital for Sick Children, Glasgow.

It is of particular interest to note the biopsy findings in those in whom three or more biopsies were performed over a relatively long period of time. Five showed endometrial tuberculosis on each of three examinations, in one instance over a period of almost eight years. In 2 further cases, negative findings intervened between positive findings, the intervening negatives numbering three in one instance. In view of this, other patients in whom only one or two negatives were obtained cannot be regarded as conclusively healed. In another 2 cases, four successive negatives were obtained, suggesting possible arrest or healing of the endometrial disease. The results of multiple biopsies indicate the difficulty of establishing criteria of arrest or cure. Moreover, there is no evidence that conversion to negative of the endometrium necessarily indicates improvement of tubal disease. It may be added that 2 further cases, in each of which only two biopsies were done, showed evidence of endometrial tuberculosis persisting after thirteen and eight years respectively.

Although it was considered most improbable that curettage of a tuberculous endometrium would 'cure' the condition, studies were carried out to observe the post-curettage recurrence of the tubercle follicles and to determine its time-interval. Four sterile patients were investigated. Tuberculous endometritis was found to have recurred at the following intervals after thorough curettage under anæsthesia: twenty days, twenty-seven days, thirty-four days and three months. The question naturally arises as to the location of the focus from which reinfection occurs. Jameson (1935) suggested that it may be from diseased fallopian tubes; indeed Solomons (1935) states that removal of tuberculous fallopian tubes means a cure of tuberculous endometritis. It was therefore decided to remove tuberculous tubes and to do follow-up endometrial biopsies in suitable cases of known endometrial tuberculosis.

Findings in 4 patients so treated, however, proved that removal of tuberculous fallopian tubes does not cure endometrial infection and that, while the tube may be a source of reinfection, it is not the only one. The suggestion therefore arises that reinfection after curettage may occur from tubercles remaining in the unremoved basal layer, or, assuming that there is a shedding of all tubercles at menstruation, reinfection may occur from infected mucus or blood in the uterine cavity. The possibility of cure of endometrial infection by curettage must be considered remote although a number of writers state this may happen.

In 238 of the series of 275 cases, tubal insufflation was performed and showed non-patency in 145 (60·9%). In the earlier cases the diagnosis of non-patency was often made as the result of a single test, the limit of pressure was 200 mm Hg. The possible fallacy of single-test negative diagnosis and its extent have been discussed by Sharman (1950). During recent years, a much more strict minimal criterion has been established as a routine in the investigation of patency: two negative insufflations and a negative hysterosalpingogram, and the limit of pressure raised to 250 mm Hg. In known cases of endometrial tuberculosis, hysterosalpingography and repetition of insufflation are now omitted as these procedures are not without risk of spreading the infection. This high incidence (60·9%) of tubal occlusion may be compared with the findings of Sutherland (1943) 80% in 20 cases; Sharman (1947) 61·8% in 89 cases; Stallworthy (1948) 50% in an unstated number of cases and Rabau (1950) 75% in 70 cases. Halbrecht (1946*a*) found 18 cases of endometrial tuberculosis in 48 sterile patients with partial or complete tubal occlusion. On the other hand, Israel & Meranze (1950) found no such infection in a study of 177 sterile patients in whom 73 (41·2%) were stated to have partial or complete tubal occlusion. Endometrium was obtained in 172 cases. In my opinion their diagnosis of tubal blockage as the result of a single test is much open to question, as also is their statement that uterotubal spasm may be eliminated as having been a factor because general anæsthesia had been employed.

Since the pathologists tell us that endometrial tuberculosis is virtually without exception secondary to tuberculosis of the tube, and since the endometrium often escapes infection even when the tubes are the seat of gross tuberculous lesions, it is certain that the incidence of tubal tuberculosis, in my series, is much higher than the recorded incidence of 5·7% of endometrial infection. It is suggested therefore that tubal tuberculosis of a degree not sufficient to be recognizable except on laparotomy – and even then often only on microscopic examination – is responsible for a much greater number of cases of tubal non-patency than is generally recognized (Sharman 1943). Since the incidence of non-patency in primary sterility cases is believed to be about 20% (Sharman 1950), and the incidence of endometrial tuberculosis in the same cases is about 5%, it seems to follow that tuberculosis is responsible for not less than 25% of cases of tubal occlusion in primary sterility. Some confirmation is suggested by my last 32 cases of primary sterility with tubal occlusion in which two negative insufflation results were obtained on separate occasions (at 250 mm Hg) 22% showed tuberculous endometritis (Sharman 1952).

A follow-up of all patients who were under observation for more than one year has shown that, of 209 traced, 4 sterile patients with endometrial tuberculosis became pregnant. One became pregnant in 1950, after no treatment: this patient was reported at the Annual Meeting of the American Society for the Study of Sterility, in 1951 (Sharman 1952). The diagnosis was made histologically only. The 3 others, in whom the diagnosis was made both histologically and bacteriologically, each had a course of treatment with streptomycin, 1 g daily for three months, to a total of 90 g, plus isonicotinic acid 200 mg twice daily orally to a total of 36 g. In 2 of them the pregnancy was tubal. The patient with the intra-uterine pregnancy is at present attending the antenatal clinic of the Royal Maternity Hospital, Glasgow.

Many have been followed up for from five to eight years and one for thirteen years. Salpingostomy has had no success. It would seem that in cases of endometrial-tubal tuberculosis the restoration of fertility is very infrequent, although Chalier (1938) stated that he did a linear salpingostomy in a patient with tuberculous salpingitis who eventually became pregnant and went to full-term; Eriksen (1947) reports that 2 of his patients with tuberculous salpingitis gave birth to children and Roulland (1947) reported two normal pregnancies in a patient who had had conservative treatment for adnexal tuberculosis. Cases of coexisting tubal pregnancy and tuberculous salpingitis have also been reported from time to time. The subject was considered in detail by Sharman (1953) who found 46 cases in the literature and added a case of his own.

The present follow-up has shown that only one death occurred from tuberculosis, in the case of the patient with a previous history of Pott's disease. The spinal infection apparently flared up later and death occurred three years after her attendance at the Sterility Clinic. Almost all the remaining patients continued in apparent good health. Very few reported any complaint other than continued infertility.

In conclusion, reference must be made to the treatment of the type of case of endometrial tuberculosis which I have described, namely, that in which there is no complaint other than sterility. As the tuberculosis in these cases is usually 'latent' or quiescent and as curettage, salpingostomy, or any other surgical procedure cannot be expected to remedy the patient's complaint, it is my view that nothing is to be gained by surgical measures. It should be pointed out, at this point, that the word 'latent' is used in the sense of being concealed or unsuspected and not as meaning inactivity of the lesion.

Several successive negative endometrial findings would appear to be necessary for a diagnosis of cure or arrest whether spontaneous or therapeutic; and we have yet to learn whether a healed endometrium necessarily reflects healing of the tubes. Whether streptomycin or any other drug or combination of drugs will prove of benefit in overcoming this type of case of infertility, only further experience can tell. Sutherland (1960) states that one must endeavour to cure the tubercular infection as one's main objective and accept the occasional pregnancy as a dividend. Of his personal series of 350 cases of tuberculous endometritis, 157 complained primarily of infertility: 13 became pregnant, of whom 4 obtained a normal full-term child. He states that early diagnosis is most important, e.g. by curettage in cases of adolescent bleeding. As far as drug treatment is concerned, he now regards eighteen months' continuous treatment as the minimum desirable.

It appears to me that the problem would best be tackled along the lines of prevention of tuberculous infection in childhood and adolescence, a view which I put forward in a paper in 1952.

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Mr Gavin Boyd (*Belfast*)

The Use of Stainless Steel Wire in the Treatment of Cervical Incompetence

In 1953 Shirodkar first described a surgical procedure carried out during pregnancy, designed to keep the cervix closed in patients suffering from cervical incompetence. His technique consisted of placing around the cervix a suture of fascia lata and, in later cases, of ½in. nylon tape by means of specially designed ligature carrying needles. Subsequently, at term, an elective Cæsarean Section was required. Since then many different materials have been used, some inserted as advocated by Shirodkar and others as advocated by McDonald (1957), who has reported a series of 70 cases using simple purse-string cervical sutures of No. 4 Mersilk, which can be removed to allow spontaneous delivery.

In this series of 60 cases, which commenced in 1957 at the Royal Maternity Hospital, Belfast, tantalum wire was first tried but, as it was too brittle, it was later replaced by stainless steel wire (34 SWG).

Selection of cases: Selection of cases was based on history alone. Patients with a history of two or more consecutive second trimester miscarriages and/or premature deliveries were included in the series. No attempt was made to establish the diagnosis of incompetence by any elaborate means, X-ray or otherwise, nor did one wait until the membranes began to bulge through the cervix. Some patients gave a clear-cut history of rupture of membranes several days before the miscarriage, whereas in others it was established that there had been previous missed abortions. The latter were not treated by suturing.

Technique: Between the 12th and 14th week of pregnancy, the patient was admitted to hospital. The following morning she was anæsthetized and the cervix was exposed using a duck bill speculum and two lateral vaginal retracters; adequate exposure was considered to be important and an assistant was required. The cervix was pulled down with a sponge holding forceps and, using a piece of stainless steel wire threaded into a cutting needle, deep bites were taken near the level of the internal os at 3, 12, 9 and 6 o'clock. The ends of the wire were then twisted in a clockwise direction until the cervix seemed to be closed. A second suture was then inserted just above the external os and again twisted. The two sutures were knotted together, about 3 in. from the cervix, and the ends cut short to prevent damage to the vaginal wall. Twenty-four hours later the patient was allowed to go home, with the instruction to report any abdominal pain, bleeding or discharge. Coitus was not prohibited, nor was any adjunctive therapy prescribed.

In patients who had previously undergone a repair operation, and in whom the cervix was found to be flush with the vaginal vault, a deep antero-posterior mattress suture, as advocated by McDonald, was found to be easier to insert than a purse-string suture.

At the 36th week of the pregnancy, the patient was readmitted and, under anæsthesia, the sutures were removed. This was achieved by cutting the suture at its neck or, if it was buried, by untwisting it in an anti-clockwise direction and pulling it out. Sometimes the cervix dilated up immediately and the patient was soon delivered, but in many cases the pregnancy went on to term.

Complications: Dunn *et al.* (1959) reported a maternal death, due to fulminating sepsis, in a patient in whom braided silk had been used. Rupture of the uterus, secondary hæmorrhage and tears in the cervix have all been recorded. In this series the worst complication occurred in a patient who was allowed to come into labour with the sutures in situ and who sustained a bucket-handle tear of the posterior lip of the cervix. Another patient suffered dysuria due, it was thought, to the suture passing close to the bladder. Several others were found to have the ends of the wire embedded in the posterior vaginal wall, but in no case did it penetrate the rectum nor do any serious damage.

Tables 1, 2 & 3 show the results and are self-explanatory.

Table 1

Results

Total number of cases	60
Total number of cases delivered	56
Total number of living children	43
	=76·8%

Table 2

Total number of cases with 3 or more miscarriages, in second trimester	29
Successes	22
	=75·9%

Table 3

Comparison of results

Author(s)	*Total cases*	*Success*	*Rate %*
Shirodkar 1953 (India)	43	34	79·4
McDonald 1957 (Australia)	70	33	47·1
Barter *et al.* 1958 (America)	22	16	72·7
Durfee 1958 (America)	22	16	72·7
Present series	56	43	76·8

Perhaps at this point it is appropriate to examine the spontaneous cure rate (Table 4). Malpas 1938, and Eastman 1947, have made mathematical calculations based on two factors:—

(1) The incidence of abortions in all pregnancies.

(2) The recurring factor in each pregnancy.

Malpas selected 18% as the incidence of abortion and 1% as the recurring factor. Eastman selected 10% as the incidence of abortion and 0·4% as the recurring factor. It must be pointed out, however, that these figures refer to all abortions and therefore do not apply to a series occurring after the twelfth week.

Table 4

Spontaneous cure rate

Number of previous abortions	*Cure rate* Malpas (1938)	Eastman (1947)
1	78·4	86·8
2	62·0	63·1
3	27·0	16·4
4	6·0	2·0

It is also appropriate to examine other treatments for habitual abortion, but again the figures refer to abortions occurring at any stage of the pregnancy (Table 5).

Table 5

Three or more previous abortions

	Cases	*Success*
No specific treatment (Bevis 1951)	32	81%
Treatment with œstrogens (Smith 1948)	60	77%
Treatment with progesterone implants (Bishop & Richards 1950-52)	32	72%
Treatment with vitamins and psychotherapy (Javert 1957)	106	81·2%

On examining the results obtained in this series of 56 cases, the following features emerge (*see* Table 6). Nine cases (16·1%) failed to reach the 28th week of pregnancy. In one of these, an early case, the sharp end of the wire penetrated the internal os and ruptured the membranes. Subsequently, all wires were knotted together and this accident has not recurred. In another case in this group, the wires were not tight enough and the membranes ruptured through them. Yet another case was not seen until the cervix was so widely dilated that success was unlikely. In the remaining 6 cases, all missed abortions, it is probable that the cause of failure was not concerned with incompetence of the cervix.

In 9 cases there was spontaneous onset of labour between the 28th and 36th week of pregnancy, necessitating the immediate removal of the wires. Thus, although the emptying of the uterus was delayed long enough to obtain a living baby, wires by themselves were not sufficient to prevent the onset of premature labour.

In 13 cases (23·2%), the patient was delivered within twenty-four hours of removal of the wires. In these cases there was one neonatal death, due to hyaline membrane disease.

In the remaining 25 cases (44·6%), there was a delay of more than twenty-four hours after the removal of the wires before labour commenced. Of these, one had a macerated stillbirth of an abnormal baby, a second had stillbirth due to a tear of the tentorium and the third patient lost her baby due to mongolism and hæmolytic disease.

Table 6

Onset of labour	*Number of cases*	*Successes*	*Failures*
Before 28 weeks	9 – 16·1%	–	9
Between 28 and 36 weeks	9 – 16·1%	9	–
Within 24 hours of removal of wires	13 – 23·2%	12	1
After 24 hours of removal of wires	25 – 44·6%	22	3

Repeat operation: 6 cases have had the procedure repeated in a subsequent pregnancy. Of these, 3 patients have been delivered and 3 are yet undelivered.

Experimental use of cervical suture in other cases: In an effort to prevent premature labour, the operation was performed on a primigravida with a twin pregnancy, who had come into labour at the 26th week of pregnancy.

The patient, however, continued with her labour and six hours later ruptured her membranes. The wires were removed at once and she had a twin miscarriage. Durfee has performed the operation six times to stop premature labour, but he failed in all 6 cases.

The procedure was also tried on a patient with a placenta prævia at the 24th week of her pregnancy. She had suffered from several episodes of bleeding and had required a transfusion. Following the insertion of the wire sutures, blood collected in the uterus and serum drained through the cervix. The uterus became tense and active necessitating removal of the wires forty-eight hours later, whereupon the patient had a spontaneous miscarriage.

As prematurity is the commonest cause of perinatal mortality in twins, it seemed reasonable to try the effects of cervical sutures in preventing the early onset of labour. A patient with a twin pregnancy was selected and sutures were inserted at the 32nd week. She came into labour at the 37th week and was readmitted at once for the removal of the wires. Shortly afterwards the membranes ruptured and the cord of the first twin prolapsed, resulting in a stillbirth. The second child was delivered alive. Both babies weighed less than 2 kg. Thus the operation did not prevent the patient coming into labour early, nor did it prevent the babies from being premature. For these two reasons, and because in plural pregnancy there is no evidence that the patient is more likely to have an incompetent cervix, the operation has not been repeated.

I would like to record my thanks to Mr George Gibson FRCS MRCOG, who first suggested the use of wire as a suture material, and who has kindly allowed me to include some of his cases. I also wish to thank Dr R M H Malone for his help in preparing this paper.

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Mr Wilfrid Mills (*Birmingham*)

Acute Appendicitis with Subsequent Infertility

Introduction

The purpose of this communication is to draw attention to a cause of infertility that may be inadequately appreciated and which is usually difficult to diagnose. Routine investigations of the infertile couple may fail to disclose the presence of pelvic adhesions when there is neither blockage nor stenosis of the fallopian tubes and there will be a natural tendency to conclude that tubal function is unimpaired when gas and contrast medium pass readily.

Pelvic adhesions do not always produce symptoms, but in cases where the ovaries or fallopian tubes are fixed to the back of the broad ligament with limitation of their normal movements fertility will usually be impaired. These adhesions are generally the result of some pelvic inflammatory process and in a most comprehensive list recently supplied by Green-Armytage (1960) no mention was made of pelvic peritonitis due to appendicitis.

Experience has shown that when an appendix abscess forms in the right iliac fossa it may ultimately resolve with a minimum of residual adhesions and cases treated conservatively before the use of antibiotics commonly showed minimal pathology when subjected to appendicectomy a few months later. When the abscess forms in the female pelvis, however, resolution does not appear to be so successful or so complete. Adhesions may become organized and permanent and these have a predilection for the ovaries and fimbrial ends of the fallopian tubes. The appearance of the pelvic organs is different from that following ascending infection due to gonorrhœa or uterine sepsis and there is seldom interstitial blockage of the tubes. Fimbrial ends may be covered by dense adhesions, but when set free they are usually found to be healthy and not indrawn. The ovaries may be completely buried in fibrous tissue which forms a mechanical barrier between ovulation and the tubes. These cases are among the more hopeful for restoration of fertility by operation.

Investigation

An attempt has been made to evaluate the importance of appendicitis as a cause of tubal dysfunction by assessing the probable cause of pelvic inflammatory trouble in cases subjected to operation. In nine years (1951-59) approximately 1,000 laparotomies were personally performed for gynæcological conditions, largely in a teaching hospital. Out of these, 51 operations were performed primarily for the relief of infertility in patients suspected of having old pelvic inflammatory trouble. These do not include cases of gross pelvic disease (such as endometriosis) in whom the possible relief of infertility was secondary to treatment for other symptoms. This total includes 15 cases of interstitial tubal blockage in which diagnosis by pre-operative salpingogram was conclusive and tubal re-implantation was performed. The remaining 36 patients form a group in which the decision to operate was far from easy.

All 36 cases had a pre-operative diagnosis of pelvic inflammatory trouble sufficient to impair tubal function, but without tubal occlusion except perhaps at the fimbrial end. The diagnosis was initially made by exclusion of other causes of infertility, coupled with an abnormal appearance of the salpingogram; this proved unsatisfactory and 2 patients were subjected to laparotomy on these criteria with no pelvic abnormality being found. After this experience a more critical attitude was adopted and greater attention was

paid to screening the patient at salpingogram studies, with repetition of the examination once or twice at monthly intervals. More recently culdoscopy has been introduced in selected cases and this has proved of great diagnostic value, so that no further 'negative' laparotomies have been performed. It is quite possible however that cases may have escaped diagnosis when associated with other infertile factors to which too much attention may have been paid.

At operation it was usually possible to make a diagnosis as to the cause of the pelvic adhesions taking the history (as supplied) into consideration in addition to the observed pathology. Two sources of error were recognized. The failure of the patient to give a history of an infected abortion was to be expected in many situations; while the presence of a diseased appendix adherent in the pelvis would not necessarily exclude an associated gonococcal infection. Table 1 shows the presumed ætiological factors.

Table 1
Probable ætiology in 34 cases of infertility due to pelvic adhesions

Salpingitis (gonococcal or abortion)	11
Appendicitis (with abscess)	8
Pelvic appendicitis (?)	5
Puerperal sepsis	3
Ectopic pregnancy	2
Follicular hæmorrhage	2
Tuberculous salpingitis (inactive)	1
Myomectomy	1
Endometriosis (inactive – minimal)	1
Total	34

Of the 8 patients who had suffered from appendix abscess there seemed to be little doubt regarding the cause of the infertility. Their ages at the time of appendicitis had been 4, 11, 17, 17, 19, 21, 21, 24, and drainage had been employed in all cases (including once vaginally and once rectally). Seven were cases of primary infertility while 1 patient aged 31 had previously had two early abortions (unintentional and uninfected) and the appendix abscess developed a few weeks after the second abortion at the age of 24. In this case there was no tubal obstruction and the X-ray salpingogram had appeared perfectly normal, but at operation both ovaries and tubes were bound down by extremely dense adhesions which did not involve the fimbrial ends of the tubes. In fact it was typical of these 'appendix cases' that the ovaries and tubes were immobilized and sometimes buried by dense vascular adhesions without intrinsic blockage of the tubal lumen. Occasionally fimbrial blockage had produced a small hydrosalpinx, but this was never bilateral.

Among the 5 cases of infertility following pelvic appendicitis (without abscess) one patient was most unusual. This was a case of unexplained secondary infertility and two X-rays had shown localized spill of contrast medium. At operation she was found to have a chronic mucocele of a pelvic appendix which had leaked sufficiently to produce a localized pseudo-myxoma of the pelvic peritoneum with innumerable adhesions preventing conception.

The other 4 patients had less certain association between the appendix lesion and the pelvic inflammatory state. These were cases of primary infertility with X-ray evidence suggestive of peritubal adhesions, but no history of pelvic inflammatory trouble. At operation in each case the appendix was found to be adherent in the pelvis and with more or less mucosal inflammation (one was full of pus and another had clearly perforated at some previous date), but the appearance of the fallopian tubes suggested the possibility of coincidental salpingitis. Tuberculous infections were excluded in all these cases.

Illustrative Cases

Case 1 Mrs L C, a trained nurse, aged 31 and infertile for six years had already been investigated elsewhere when first seen in 1951. Tubal insufflation had been positive and a normal salpingogram had been reported. Attention was focused primarily on hormonal deficiency as she reported several occasions of six weeks of amenorrhœa suggestive of early abortions. Eventually the X-ray was repeated and appeared to show loculation of the spill round the fimbrial end of one tube; her history of pelvic abscess drained by colpotomy after appendicectomy at the age of 21 seemed significant, but laparotomy was delayed until the endometrium had been reported negative for tuberculosis. At operation gross vascular adhesions involved small bowel and omentum as well as the tubes and ovaries, so that the necessary dissection was difficult and hæmorrhagic and the prognosis was considered to be poor. Conception occurred four months later and a second child was born three years after the first. This was the first case in the series and the gross nature of the pelvic pathology contrasted strongly with the normal results to the conventional tests for fertility.

Case 2 Mrs G P, aged 32, had had five years of infertile married life when investigated in 1958. The only abnormality that could be found in either partner was some irregularity of ovulation with corresponding lengthening of some of the menstrual cycles. Tubal insufflation was positive and X-ray salpingogram entirely normal, with rapid flow of contrast medium through the tubes. Acute appendicitis with peritonitis had been treated by appendicectomy and drainage when she was 17 and the abdominal wound had been slow to heal. As culdoscopy was not available, and there seemed no other way of confirming the suspicion of pelvic adhesions, laparotomy was undertaken, albeit with some hesitation. The pelvic organs appeared normal until the ovaries were seen to be encased in

fibrous adhesions behind the broad ligaments preventing any ovum from gaining access to the tubes, which appeared to be healthy. The adhesions were separated freely but conception has not yet occurred.

Although at least 9, and possibly more of these 34 patients would seem to have become infertile as a result of appendicitis, these figures can have little statistical significance. The patients attended a general gynæcological out-patient department and were referred from a number of sources. A particular interest was taken in 'surgical' causes for infertility and patients with a history of acute appendicitis were subjected to special scrutiny. For these reasons it is impossible to give any percentage of infertile couples in whom relevant lesions attributable to appendicitis might be found. It is suggested however that culdoscopy is an essential part of the investigation of infertility when other tests yield negative results, and also that patency of fallopian tubes as shown by insufflation and salpingogram is not sufficient to exclude disorders of tubal function. A history of peritonitis associated with appendicitis should serve to rouse particular suspicion regarding organic pathology in the pelvis.

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Mr John Stallworthy (Oxford) said that Dr Lee Buxton had recorded a major breakthrough in knowledge of the hormonal control of ovulation, and he congratulated him on his success, especially since in 1940 an extensive clinical trial had been conducted at Oxford on the stimulation of ovulation in the human adult female based on the successful animal experimental work of Rowlands and his team. This trial had failed, and the reason for the failure had now been made clear by Dr Lee Buxton. His success in the human was achieved with human pituitary gonadotrophin and as a result he had emphasised the need for species specific gonadotrophins.

Dr Buxton's paper gave a scientific explanation for the sensational claims made in the press for a 'new cure for sterility'. Mr Stallworthy, however, thought it opportune to sound a note of warning, for as he said there is no cure for sterility because sterility is not a disease. It is a symptom complex. Before any treatment is prescribed every allegedly infertile couple should have a basic minimum of investigation to determine whether there are factors responsible for delayed conception. In a small minority failure will be due to a sustained arrest of ovulation, and to this small minority Dr Lee Buxton offered new hope.

Mr Stallworthy said that Dr Sharman had reminded him of another small group suffering from unsuspected genital tuberculosis, but he was too pessimistic about the results of treatment. The new antibiotic techniques have effected a revolution in this field. In Oxford in a series of patients with endometrial tuberculosis proven bacteriologically, treatment had been followed by 12 pregnancies of which 7 continued successfully to term. There were 2 abortions and 3 ectopic pregnancies.

Mr Stallworthy appreciated Mr Gavin Boyd's account of the success of his fuse wire cervical suturels, and also Mr Mills' survey of the possible ætiological significance of acute appendicitis in disturbing tubal function. Mr Mills had stated that in spite of a normal salpingogram there may be adhesions and loculations involving the ovary and fimbrial end of the tube. If he said these could be present in spite of a radiologist's report of a normal salpingogram Mr Stallworthy would agree with him. He felt it is not uncommon to find in studying films *reported* to be normal that there is in fact evidence of loculation, and he would reserve judgment on any statement that significant adhesions can be present in spite of a normal salpingogram. He would appreciate the opportunity of studying such films with Mr Mills which might prove him to be wrong in believing that with experience it is possible to diagnose loculation radiologically. Mr Stallworthy felt that the question was of more than academic interest because if the view of Mr Mills is correct there would be a place for pelvic exploration or culdoscopy whenever infertility was associated with a history of acute appendicitis even if the tubes appeared normal on salpingography. On the evidence submitted he felt that he could not accept the proposition but would reserve judgment until after he had studied the matter further.

Mr Stallworthy added that most patients complaining of infertility were not necessarily infertile. The injections advocated by Dr Lee Buxton and the sutures recommended by Mr Boyd could achieve miraculous results in carefully selected patients. In all others they would be unnecessary. The task of clinicians is to investigate before prescribing, and to remember that investigations will confirm that most enquiring couples require nothing more than reassurance.

Mr V B Green-Armytage (London) expressed his pleasure at hearing the references by Dr Lee Buxton to the hypothalamus in its relation to infertility for it reminded him of an eloquent paper read on this very subject by his old friend, Geoffrey Theobald, many years ago. He wished to protest against routine endometrial biopsies; though 20% of all infertile patients had obstructed tubes, and of these 5% were due to tuberculosis, these were the only proper cases for such biopsy.

Not more than 64% of women ovulated regularly every month. Therefore there was no valid reason for biopsies unless they were repeated at least twice or thrice to be accepted as negative, and these should be done properly under anæsthesia.

Routine endometrial biopsy now tended to become a money spinning racket at the cost of much money from the patient or to the National Health Service. Therefore as in *more* than 50% of patients a potentially dangerous and painful procedure could be substituted by proper investigation of the cervical mucus

between the 12th and 14th day of the cycle, such as the Spinnbar Test, the Vaginal Smear, the Fern Test, the Clinistix Test and Occult Blood Test, to say nothing of the basal temperature chart he would warn the audience from accepting or attempting routine biopsy which was a test only necessary in well *under* 50% of cases.

Moreover, he would remind them that the records of a great number of hospitals indicated that there was in roughly 6% of patients who had had endometrial biopsy a story of low grade fever suggesting ascending infection with the possibility and probability of mild salpingitis with subsequent infertility due to glueing of the fimbriæ, or plicæ of the endosalpinx. Finally he showed a short sound film of the new medico-surgical approach to the problem of occluded tubes.

Dr A A Loeser (London) said that nervous conditions, especially shock, were very often the cause of anovulatory menstrual cycles, although the anatomical state of the anterior pituitary was normal.

The regulation of the anterior pituitary depended absolutely on the hypothalamic centres and their connexion with the forebrain.

In psychiatric cases this regulation of the pituitary was often abolished, as could be seen in mental patients. In shock patients, the hypothalamic pituitary 'clock' came to a standstill and no ovum ripened, which was proved by curettage of the patients many weeks after the shock (Loeser & Novak 1943).

In London, with the gynæcologist Kurt Stern, Dr Loeser had made the following experiment. They went to slaughter houses, removed aseptically the anterior pituitary from calves, and implanted the anterior lobe into women who had from time to time only scanty anovulation periods. In 2 cases of anorexia nervosa there was no result, but in cases where the nervous symptoms were not in the foreground, menstruation with ovulation took place for two to three months, until the implant was absorbed.

Afferent nervous stimuli from the cervix could also bring about a refunctioning of the pituitary and produce ovulation, where none existed before. Sometimes in women, even the sight of the man they love can make them ovulate, whereas the unloved husband cannot. Extramarital intercourse can prevent ovulation (anxiety complex).

It was clear from this that the anterior pituitary produced the gonadotrophic hormones in the proper amounts *only* when the nervous pathways originating in the hypothalamic centres functioned well. As soon as these pathways were disturbed or interrupted, no normal ovary or endometrium could bring about proper menstruation or ovulation.

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Professor W C W Nixon said that he had had the privilege of seeing Professor Ernest Page (1958) at San Francisco do his operation of 'wrapping' the cervix. Since that occasion he had personally performed this operation 6 times and 4 living babies had been delivered. He had recently heard from Professor Page that he has a total of 18 cases and the overall success rate as measured by living children was 13 with 4 failures and one patient who was not yet pregnant because the operation was fairly recent. These results were about the same as other methods of treatment but one thing he was sure about was that there was no impairment of fertility and the procedure did not require cæsarean section.

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Section of Otology

President J P Monkhouse FRCS

Meeting December 2 1960

Discussion on Intracranial Complications of Otogenic Origin

Mr Joe Pennybacker (*Oxford*)

We have had something over 200 patients in the Department of Neurological Surgery at the Radcliffe Infirmary with intracranial complications of mastoid infection (Table 1).

Table 1
Intracranial complications of mastoid infection

	No. of patients
Temporal lobe abscess	55
Cerebellar abscess	30
Otitic hydrocephalus	28
Cerebral thrombophlebitis	14
Meningitis	13
Subdural abscess (middle and posterior fossa)	10
Lateral sinus thrombosis	8
Extradural abscess (middle and posterior fossa)	5
Osteitis of skull	3
Endaural cerebral hernia	2
Cerebrospinal otorrhœa	1
Subgaleal aerocele	1
Undetermined	35

This is selected material in the sense that all these patients have been referred to a neurosurgical department under suspicion of having intracranial complications which the otologist does not commonly deal with, and this explains the fact that there have been comparatively few cases of lateral sinus thrombosis, extradural abscess and meningitis. It also explains the large number of cases in the undetermined group. These are mostly patients who have headache, giddiness or some other symptom consequent on mastoid infection; all our special investigations are negative and the patients usually recover. Our function with this group is thus largely an excluding one.

But if this is selected material, I should also say that I have seen most of the intracranial complications which have occurred in the Ear, Nose and Throat department at the Radcliffe Infirmary. In fact, there have not been many, and the volume of our material is derived from our being the only neurosurgical centre in our region. The actual incidence of each complication is not of great importance: the fact is that meningitis, brain abscess, sinus thrombosis and otitic hydrocephalus are comparatively common, whereas the other listed complications are comparatively rare.

In the vast majority of cases intracranial complications are the result of direct spread of the infection. On only two occasions, for instance, have I seen a brain abscess due to mastoid disease in an unusual site: one was a child who died with an abscess in the thalamus, and this must have been a hæmatogenous one from a bacteriæmia at some stage in her illness. The other was an abscess in the postero-medial part of the lateral lobe of the cerebellum, which arose by extension of an infective thrombosis of the lateral sinus along one of the tributary veins from the cerebellum.

The locus of the infection is determined by tissue planes, and otologists are familiar with cellulitis of the scalp overlying an infected mastoid, and with subperiosteal abscess. Infection of the mastoid may extend to involve the petrous bone commonly, and the vault of the skull more rarely. Collections of pus in the extradural space, either in the middle or posterior fossa, are common findings at mastoid operations and may mark the limit of the infection or may be associated with infection in deeper planes, e.g. subdural abscess, leptomeningitis, and brain abscess. Proximity of the transverse sinus renders it an easy prey to thrombosis, and this may extend back along tributaries from the cerebrum and cerebellum to disturb the circulation and cause alarming neurological symptoms such as epilepsy, profound paralysis, aphasia and the like. Com-

monly the infection is active in two or three of these planes: thus a patient may have an extradural abscess, a subdural abscess and meningitis at the same time. Or one or more planes may be missed out, or apparently so, as not infrequently a person with a temporal lobe abscess has no evidence of extradural or subdural abscess, and no meningitis.

Diagnosis and Treatment

Most otologists have their own personal standards by which they judge whether a mastoid infection is behaving properly or not. They know how much local pain is allowable, for how long and to what extent the temperature may be elevated, and so on. But undoubtedly the common use of sulphonamides and antibiotics influences the constitutional reaction in such a way that intracranial complications can occur with little evidence from the temperature and pulse chart, and to this extent the problem is more difficult than it once was.

Mr J D K Dawes (p. 315) stresses the importance of headache as a symptom, and rightly so, because headache can be the earliest and most constant feature of all these complications. Its most serious significance is when it is a symptom of increased intracranial pressure, and then it is often accompanied by nausea and vomiting, later by drowsiness going on to stupor, coma and death if unrelieved. Sometimes it is a factor of meningeal irritation, as in meningitis or subdural abscess, and sometimes it is due to no cause that we can determine. Many of the patients in the 'Undetermined' group in Table I were referred to us as brain abscess suspects because of headache following a mastoid infection, and our investigations proved entirely negative. It may be very difficult to assess headache in children, and in very ill patients who may be so ill in other respects that they are unable to describe their headache. And so we cannot rely entirely on headache for the detection of intracranial complications, nor can we exclude them by its absence.

Giddiness is another common symptom, but here the neurosurgeon is on less familiar ground than the otologist. Whether it is a feeling of unsteadiness or frank vertigo, I am rarely certain whether it is due to labyrinthine irritation by the disease process (or operative intervention) or whether it has a more central and serious significance. I think all I can usefully say is that it is very common in cerebellar abscess and may indeed be the predominant symptom.

Fortunately in lumbar puncture we have an easy method of getting information about the intracranial pressure, what is happening to the meninges, and whether or not the lateral sinus is patent. This is the first special investigation to be undertaken in cases of mastoid disease which are not going well. It may establish the diagnosis of meningitis at once, and enable treatment to be started, or it may show the increase in pressure and the slight increase in the protein content and cell count of the fluid, which are common in brain abscess and in some cases of subdural abscess. It may reveal the high pressure and the watery or normal fluid which are common findings in otitic hydrocephalus. A normal spinal fluid does not exclude any of these possibilities (except meningitis) as in a few cases of brain abscess (less than 5%) the fluid may be normal, and also in occasional cases of subdural abscess – and this is remarkable when we see that a large collection of pus is separated from the subarachnoid space by the very thin arachnoid membrane.

The dangers of lumbar puncture are well known, but I think they have probably been overstressed, and the value of the information which may be gained outweighs the risks. Lumbar puncture is only dangerous in advanced cases of increased intracranial pressure, when there is violent headache, stupor or coma, and in such there is often papillœdema as well. In these cases, the puncture had better be done in circumstances where an immediate operation can be done if necessary, this usually means neurosurgical facilities.

Ordinary X-rays of the skull may also yield useful information. They may show evidence of osteitis, and in children appearances associated with increased intracranial pressure such as separation of the sutures and convolutional thinning of the vault. In adults the pineal gland may be calcified, and if this is displaced from the middle line it is a considerable argument for an expanding lesion such as an abscess in one cerebral compartment.

Evidence of more localizing value may be obtained from cerebral angiography. Displacement of the normal arterial pattern may reveal a subdural or temporal lobe abscess, or indicate the ventricular dilatation which occurs with cerebellar abscess. The phlebogram may show partial or complete occlusion of one of the large venous sinuses. In skilled hands, angiography is quite safe and rarely upsets the patient or adds to the urgency of his condition. The same cannot be said of ventriculography or air encephalography which, although valuable diagnostic methods, often aggravate matters to the point where immediate operation is imperative. These investigations should only be carried out where neurosurgical facilities are available, but these techniques may reveal lesions not detectable by other means, and they are of particular value in the final exclusion of a space-occupying lesion.

Electroencephalography is also of value in some cases and may reveal an abnormal electrical

discharge in relation to an abscess, which some regard as almost diagnostic, but in our experience the EEG has not been reliable to that extent.

Common Intracranial Complications

Of the complications which have not already been dealt with, brain abscess is the most important. *Abscesses due to mastoid disease* have a very constant situation in the middle third of the temporal lobe or in the anterior part of the lateral lobe of the cerebellum. The temporal ones are adherent to the dura over the tegmen tympani, and the cerebellar ones are adherent to the back of the petrous bone in the region of Trautman's triangle. In either situation – and we have had one case with abscesses in both sites – the abscess produces two groups of effects, those due to increased intracranial pressure, and the focal symptoms and signs due to the part of the brain affected. The general symptoms of increased pressure are due partly to the size of the abscess but also, in the early stages in particular, to considerable œdema of the brain surrounding the abscess. This causes headache, nausea, and vomiting, and if unrelieved there is stupor, coma and death, a picture that the older otologists will remember all too well. As I have said, this general picture may be somewhat modified nowadays by the common practice of administering antibiotics and sulphonamides, and an abscess may develop very subtly. It is for this reason that lumbar puncture is of such great value in the early stages of the development of an abscess because it will often reveal a significant but not dangerous increase in pressure and it will almost always show an increase in the protein content and cell count of the fluid. In the later stages, of violent headaches and stupor, when lumbar puncture may be dangerous, there is often papillœdema, but generally it takes two or three weeks for this to develop, and about the same time for the skull sutures to separate in children.

The focal signs of a temporal lobe abscess may be very slight and inconspicuous or highly eloquent, especially if the abscess is in the speech-dominant hemisphere, because some degree of aphasia is very common. This may be slight in degree, the patient only making an occasional mistake in speaking, or using unusual words, or having difficulty in finding the right word. Or it may be so gross that the disordered speech is taken as evidence of dementia and the patient is sent to a mental hospital. The next most common neurological sign is a defect in the visual fields. Because the lower fibres of the optic radiation sweep down in a loop through the temporal lobe, an upper quadrant hemianopia occurs. It may only be possible to detect this on careful perimetry, but in cases of suspected temporal lobe abscess, it is worth doing this because it is almost diagnostic. As the abscess increases in size the hemianopia may become complete and it can then usually be detected by confrontation tests at the bedside. Gross paralysis and sensory defect down the opposite side of the body are uncommon, but as the face and arm are represented in the lower part of the rolandic area, some weakness of the face and arm on the opposite side are the earliest defects to show themselves. It will be seen, thus, that an abscess in the non-dominant temporal lobe may be relatively silent, as the visual field defect may not be detected and the sensorimotor disturbance may be very slight.

In the cerebellum, on the other hand, the signs are more definite. As noted above, headache may be accompanied by insistent giddiness or vertigo. There is often stiffness of the neck, and the head may be held in an unusual posture, tilted to one side or bent forward almost as though to pull the cerebellar tonsils out of the foramen magnum where they are being pushed by the expanding abscess and surrounding œdema. There is usually nystagmus which is slow and coarse on looking to the side of the lesion and rapid and fine on looking to the opposite side. The limbs on the side of the lesion are ataxic in purposive tests, and if the patient can still walk, his gait is unsteady. In the later stages, the speech may become a little thick and slurred and there may be difficulty in swallowing.

When any of these signs, or any combination of them, suggest the possibility of a brain abscess, steps should be taken to confirm or exclude such a lesion. As noted above, lumbar puncture may provide supporting evidence. In the cases of temporal lobe abscess, ordinary X-rays of the skull may show displacement of the pineal gland to the opposite side, and the EEG may reveal a focal discharge. More certainly, a carotid angiogram will show a characteristic upward displacement of the middle cerebral group of vessels. If facilities are not available for this, a ventriculogram will reveal an expanding lesion in the temporal lobe, but as this method may have to be followed by immediate operation on the abscess, it should be deferred until such an operation is possible. Ventriculography is the only special investigation which gives much help with cerebellar abscesses, and it is usually the immediate precursor of operation on the abscess.

The treatment of a brain abscess nowadays is fairly straightforward. Having diagnosed and localized it, a burr hole is made over it and the pus is aspirated through a blunt brain cannula. We then instil 500,000 units of penicillin and 2 c.c. of a radio-opaque solution (either Thorotrast or Steripaque) so that the exact size and situation of the abscess can be followed in X-rays taken at intervals of two to three days. This initial

aspiration usually brings about a striking improvement in the headache, stupor and focal signs, but when and if the headache recurs and focal signs reappear, or when X-rays show that the abscess is larger, another aspiration is done. For the first three or four days the blunt cannula can be pushed through the wound; thereafter a sharp needle has to be used. As a result of these aspirations, there is usually a steady improvement and this means one of two things, that the abscess is shrivelling up, or that it is developing a thick capsule and the surrounding œdema is lessening. The X-rays will tell which is happening, and if the abscess shrivels up to become a small crenated mass, most surgeons would prefer to leave it alone. But before the patient is allowed to go home, as cured, two conditions should be met; a final lumbar puncture should show that the pressure is normal and that the C.S.F. is normal on analysis; and an air encephalogram should be done to show that the ventricular system is normal, and that no undiscovered loculus of the abscess is present.

On the other hand, if the abscess continues to expand after, say, four or five aspirations, it ought to be excised. By this time, usually four to five weeks after the onset of the infection, it has a thick enough wall to allow it to be dissected out of the brain much like a subcortical tumour.

This method of treatment is applicable to most brain abscesses and it has been evolved over the past twenty-two years, with a progressive improvement in the results as set out in Table 2.

Table 2
Brain abscess due to mastoid infection

	1938–1950			1950–1960		
	No. of cases	*Deaths*	*%*	*No. of cases*	*Deaths*	*%*
Temporal lobe	31	10	32	24	1	4
Cerebellum	19	8	42	11	1	9
Total	50	18	36	35	2	5·7

This account of the diagnosis and treatment of a brain abscess may make both sound almost too easy. I realize that this is very far from the case, and that mastoid disease is being dealt with today in hospitals where the facilities are considerably less elaborate than at the Radcliffe Infirmary. There is the otologist, X-ray equipment, and an operating theatre, but no facilities for perimetry, electroencephalography or angiography, and indeed no neurologist or neurosurgeon. And I suppose that is why we are having this discussion to-day, i.e. to help the ear, nose and throat surgeon who has, or thinks he has, a brain abscess on his hands. My advice is quite simple: as the definitive treatment of a brain abscess is a neurosurgical problem, the patient should pass into neurosurgical hands as soon as possible. Moving the patient to a neurosurgical centre means, of course, that he is fit to travel and that a neurosurgical bed is available. In most cases there is no difficulty in deciding about the former, but if the patient is stuporous or comatose or getting worse rapidly, it is not advisable to send him on a long ambulance journey. In these circumstances, it is worth giving urea intravenously. This has a remarkable effect in reducing intracranial pressure and is quite safe. It is given in doses of 1g/kg of body weight in a solution of invert sugar and the effect is manifest within fifteen to twenty minutes. It persists for several hours, and may thus make it possible to move a seriously ill patient with reasonable safety. If the urea is not effective, i.e. in bringing the patient out of stupor, something must be done on the spot and the right thing is to make a clean burr hole in the squamous temporal bone just above the ear, put in a brain cannula and try to aspirate the abscess. In the cerebellum, the burr hole should be made just below the tranverse sinus and midway between the mastoid process and the external occipital protuberance. This needs only three instruments not commonly included in the otologist's kit, a perforator, burr and a brain cannula, and no modern surgical theatre should be without them, even though they are not much used. If the abscess is found, 500,000 units of penicillin in 1 c.c should be injected, and if Thorotrast or Steripaque is available, 2 c.c. of this should be instilled as well, and the wound closed. This is a life-saving procedure and may provide twenty-four to forty-eight hours' safety in arranging transfer to a neurosurgical centre. If there is difficulty or delay in getting into one centre, another should be tried; most neurosurgeons are ready to co-operate.

The critical situation which I have just described may develop rapidly in a mastoid infection under observation in hospital, or the patient may be sent into hospital in such a state, or it may develop after operation. In the first two possibilities, there may be doubt as to which should be dealt with first, the brain abscess or the mastoid. If the patient is in stupor or coma, his life is at risk from increased intracranial pressure and the abscess should be aspirated first, but the mastoid should be done as soon thereafter as possible, i.e. when the patient has recovered from the pressure effect. This may be within a few hours or the next day. If the patient is not so ill, and the diagnosis is in some doubt, it is usually safe to proceed with the mastoid operation and see what effect this has before going any further.

In any case, I would urge again the importance of seeking for a brain abscess through a clean burr hole and with a brain cannula rather than sinus forceps. If these manipulations are carried out through a mastoid wound there is a considerable risk of a cerebral fungus developing, either behind the ear or in the external auditory meatus, depending on the approach to the mastoid. The endaural fungus may be accompanied by cerebrospinal otorrhœa, and this usually means an intracranial operation to seal off the fistula.

If an abscess is not found neurosurgical help becomes more urgent, and may be unavailing, but occasionally ventricular drainage or a decompressing operation may tide the patient over until the diagnosis is established. In this small group there are occasional cases of coincidental mastoid infection and brain tumours, vascular accidents, or metastatic abscesses – all of which we have seen.

Another complication which may look alarming but is fortunately benign is *otitic hydrocephalus*. This is essentially a disease of children and young adults, but can occur at any age. It is thought to be due to defective absorption of cerebrospinal fluid such as might result from thrombosis of one or more of the large intracranial venous sinuses impairing the efficiency of the arachnoid granulations. The clinical effect is to raise the infracranial pressure and this causes headache, papillœdema and elevation of the spinal fluid pressure. These effects may be apparent during the course of a middle ear or mastoid infection or may come after the infection has apparently subsided. It is probable that many cases are undetected, because the pressure effects are rarely critical; headache may be present for a few days, but is not severe, the patient usually looks and feels well otherwise, and only if the optic fundi are examined and a lumbar puncture is done can the fact of increased pressure be established. In most cases, the appearance of a squint due to paralysis of one or both VI nerves leads to the detection of papillœdema and this immediately raises the question of a brain abscess. Such cases need full investigation: although well-being is characteristic of otitic hydrocephalus, I remember a little boy who was apparently quite well with a chronic abscess in the right temporal lobe which contained 100 c.c of pus. Apart from a VI nerve paralysis, there are usually no focal neurological signs in otitic hydrocephalus. The spinal fluid pressure is raised but usually not to the extent which would be expected from the degree of papillœdema: pressures of 200–250 mm are common, whereas in brain abscess pressures of 300–400 mm are usual. The cerebrospinal fluid moreover, contains no cells and usually less protein than normal, i.e. 15–20 mg%. X-rays of the skull and the EEG may be normal. But to exclude an abscess we usually do a carotid angiogram in the first place, and if this is normal, we finally exclude an abscess by a ventriculogram or air encephalogram. When the diagnosis is established, no treatment is called for, as the symptoms usually subside within two or three weeks. The papillœdema may take two or three months to resolve, and a close watch needs to be kept on the visual acuity as, if there is any evidence of deterioration, a decompression operation may be necessary. One little boy in this series lost his sight despite such an operation, but this is the only case in which this has happened.

Cerebral thrombophlebitis may result from a backward extension of thrombosis in a large venous sinus, or it may occur in the course of a mastoid infection not known to be complicated by sinus thrombosis. It also occurs in association with *subdural abscess* and in practice it has to be differentiated from this condition. The spread of thrombosis to cerebral veins is usually signified by the onset of focal epileptic attacks involving one side of the body, and these may occur at such frequent intervals that there is virtually status epilepticus. When the fits have subsided, the patient will be found to be drowsy and the functions of the affected hemisphere will be largely in abeyance. That is to say that in the non-dominant hemisphere there is hemianopia, hemiplegia, and hemianæsthesia, and to this in the dominant hemisphere is added aphasia. This may all happen within a few hours, too rapidly for a brain abscess, for instance. In some cases, the patient does not seem to be as ill as the neurological picture would suggest, and he will probably have an uncomplicated thrombophlebitis from which he will recover. In others there is a severe mastoid infection with general illness, and in these the thrombophlebitis may be a feature of subdural abscess. In either case, the cerebrospinal fluid is not of great help: it may be normal or it may contain a slight excess of protein and a few cells. The most valuable investigation is angiography which will either be normal, or will reveal a subdural collection. These cases often present as emergencies, and in practice we often make exploratory burr holes to exclude a subdural abscess, and follow this with a deliberate angiogram at a later stage to exclude an intracerebral abscess.

If a subdural abscess is found, a number of burr holes are placed in the skull, up to 6 on one side, and small tubes are placed in the subdural space partly for drainage but chiefly to allow the instillation of penicillin. Although this is one of the most serious complications of mastoid disease, if it can be detected early and is due to organisms sensitive to penicillin, recovery is possible.

Fig 1A

Fig 1B

In conclusion, the following case which appeared unique, may be of interest but whether it was a mastoid infection or injury I am not certain.

Case Report: The patient (R.I.241196) was 33 years old, and came to us in May 1957. In 1948 he had a right-sided middle ear infection with discharge for about three weeks. This resolved and had not recurred. In 1954, he received a blow in the right frontal region which lacerated the scalp but there were no intracranial complications, and the wound healed normally. The only other point in his earlier history was that he had osteomyelitis of the tibia at the age of 11.

In January 1957 he became aware of a soft swelling in the right parietal region which varied in size from time to time and caused few symptoms. He ultimately got into the hands of the late Mr R R Simpson of Hull, who had some X-rays taken and these showed an extensive mottled erosion of the right side of the vault (Fig 1). The Wassermann reaction was negative, and there was no constitutional evidence of infection.

The scalp swellings (Fig 2) were found to contain air and it seemed likely that this was escaping from

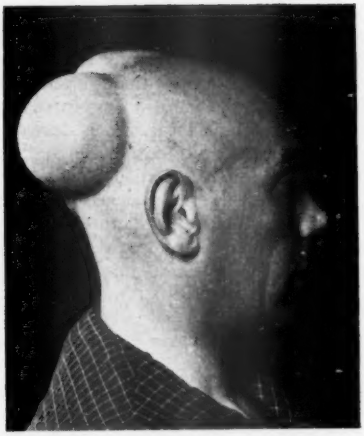

Fig 2A

Fig 2B

the mastoid. Mr R G Macbeth and I explored this and found an appearance of the skull vault which I had never seen before: a mottled erosion in places involving the whole thickness and exposing the dura and in other places apparently confined to the inner or outer table. Islands of normal looking bone were seen in the midst of the affected area, and in all it seemed to be neither neoplastic nor inflammatory. Histological examination did not take us much further, except to exclude these possibilities. In any case, Mr Macbeth found a hole in the mastoid which he plugged with a little flap of temporal muscle, and this was effective.

The possibilities are, I suppose, that this was some kind of bony dystrophy which eroded a mastoid cell and allowed the escape of air under the scalp or that the injury fractured a previously

infected cell, and the changes in the bone were due to the pressure of the trapped air.

In recounting these various pathological states, I hope I have made it clear that there is much that the otologist can do alone, but there are some cases in which collaboration with the neurosurgeon is to the general advantage. I have stressed this point on other occasions, but it is more nearly practicable now than it has ever been in the past. There must be few otologists who have not some kind of liaison with a neurosurgical centre, and these I would advise to establish such contact as soon as possible.

Mr J D K Dawes (*Newcastle upon Tyne*)

199 cases of otogenic intracranial complications admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, during the years 1944–1960 are analysed to show the results of treatment, to determine the major remaining problems of clinical practice, and to draw attention to faults in management.

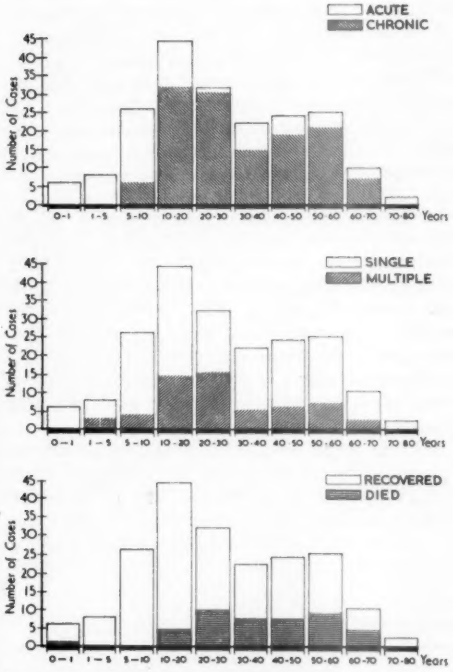

Fig 1 *The age incidence of otogenic intracranial complications*

Fig 1 shows that the greatest incidence of otogenic intracranial suppuration occurs in the 10 – 20 age group, although the lesions occur at all ages. As expected, acute ear disease is the commoner cause in childhood and chronic ear disease in the adolescent and adult. Comparing the three graphs suggests that a multiplicity of intracranial lesions and death more commonly follow chronic suppurative otitis media.

Fig 2 stresses the great improvement in the mortality rate over the years, although the incidence of intracranial suppuration has only recently become slightly less. This improvement is undoubtedly due to the more efficient use of antibiotic therapy. One of the 4 deaths during the past seven years was that of a 1-month-old child who died from an undiagnosed extensive intracranial sinus thrombosis. Throughout this series the highest death-rate has always occurred in those patients with multiple intracranial complications of chronic ear disease (as marked by circles in Figs 2, 3 & 4). Using a similar method I will now consider the major intracranial complications individually (Figs 3 & 4).

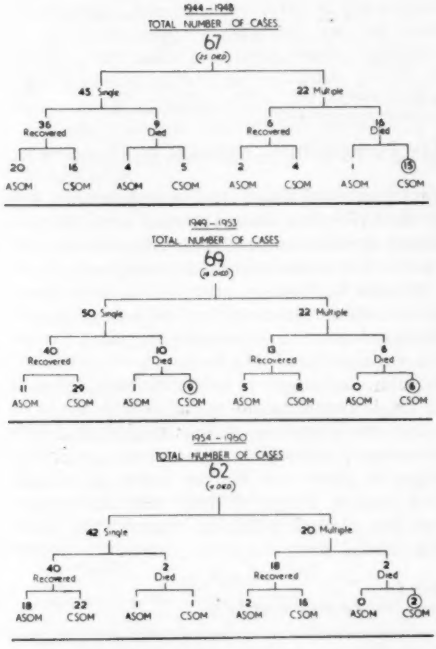

Fig 2 *The incidence of the varied types of otogenic intracranial suppuration and mortality rate grouped according to the years of occurrence*

97 patients had proved intracranial sinus thrombophlebitis, 89 being confined to the lateral and transverse sinuses or jugular bulb, and in three of these the thrombosis had extended into the

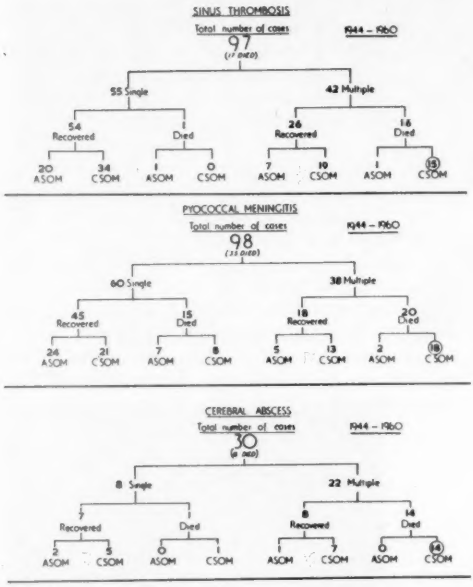

Fig 3

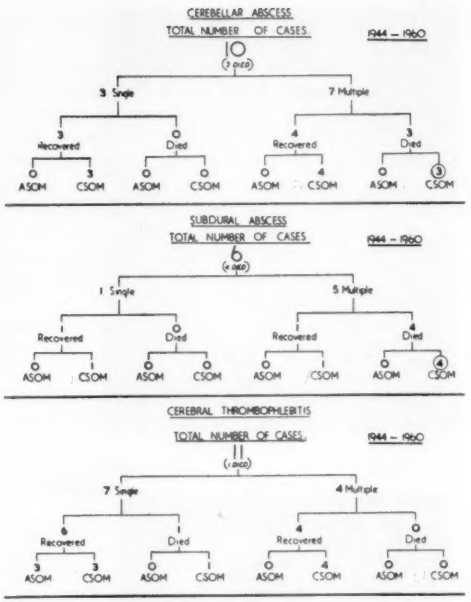

Fig 4

Figs 3 & 4 *The incidence and results of treatment of each major type of intracranial complication*

superior petrosal sinus, and in one beyond this into the cavernous sinus. Included are 7 cases of isolated superior petrosal sinus thrombosis, one of which had extended into the cavernous sinus. 55 patients had involvement of the intracranial venous sinuses alone with or without perisinus abscess, whereas in 42 patients the sinus thrombosis was associated with lesions in the cerebrum, cerebellum, meninges or subdural space. When it is a single complication of ear disease, acute or chronic, the prognosis of sinus thrombophlebitis is excellent, provided that correct antibiotic therapy is given and the ear lesion is brought under control. Rarely is there need for surgery when the thrombophlebitis complicates acute otitis media, since vigorous antibiotic therapy controls the intracranial complication as well as the ear disease. Consequently sinus thrombophlebitis may be suspected but infrequently diagnosed as an isolated complication of acute ear disease. 5 cases of otitic hydrocephalus occurred in the series; all recovered and all were associated with sinus thrombophlebitis. Control of the meningitic and cerebral abscess group has been much less effective and the high mortality requires explanation.

In this series no case of cerebellar abscess or subdural abscess was found to complicate acute ear disease. The mortality rate of subdural abscess was high because the diagnosis was made just before death or at autopsy. It is worth noting that 6 of the 7 cerebellar abscesses in the multiple

Table 1

Causes of death in otogenic meningitis

	Uncontrolled infection	*Late diagnosis*	*Unexplained*	*Mismanagement*
A.S.O.M. 9 deaths	6 (all prior to 1949)	2 moribund	1	
C.S.O.M. 26 deaths	6 (5 Prior to 1947)	15 { 4 moribund; 8 temporal lobe abscesses; 2 cerebellar abscesses; 1 subdural abscess }	3	2

Table 2

Causes of death in otogenic temporal lobe abscess

	Uncontrolled infection	*Late or no diagnosis*
1944–1948 8 deaths (62% mortality)	3 { 2 pyæmias; 1 meningitis }	5 { 1 moribund; 2 meningitis; 1 subdural undiagnosed; 1 undiagnosed }
1949–1953 5 deaths (71% mortality)	1	4 { 1 moribund; 2 meningitis with late diagnosis; 1 pyæmia }
1954–1960 2 deaths (22% mortality)		2 Both meningitis with late diagnosis

group and all cases of cerebellar thrombophlebitis were associated with and presumably were consequent on lateral sinus thrombosis. The prognosis in cerebral and cerebellar thrombophlebitis is excellent; the only death, and this in 1944, was caused by a phlegmonous encephalitis.

Once again these figures stress the importance of the multiple intracranial lesion complicating chronic ear disease.

Seeking to explain the overall high mortality, a more detailed method of analysis has been used, and I have chosen to show the results of this in meningitis and temporal lobe abscess (Tables 1 and 2). All the uncontrolled meningitic infections occurred early in the series when the antibiotics were given in small dosage and their variety and efficiency were limited. Several patients were sent into hospital moribund and on other occasions the presence of a lethal lesion such as cerebral abscess or subdural abscess remained undiagnosed and untreated. Pyococci were found in the cerebrospinal fluid in only 28 cases and in 2 of those who died *B. pyocyaneus* was also cultured. The finding of bacteria in the cerebrospinal fluid did not appear to influence the mortality rate and the low incidence may be because the patients were given chemotherapeutic or antibiotic agents prior to admission. Similarly the deaths of patients having temporal lobe abscess (of whom 50% died) were caused by uncontrollable infections, particularly in the early days, or a failure to make a diagnosis at least till late in the illness. Physical signs of severe meningeal irritation often obscured the diagnosis of a brain abscess until the meningitis was largely under control. Unfortunately the meningeal irritation in some was a leaking brain abscess, particularly when the meningitis had been preceded by more than a week's history of headache and vomiting. The patient whose abscess leaked into the ventricle as illustrated by Thorotrast in Fig 5 had a history of six weeks' earache and four weeks' headache and vomiting prior to the sudden development of a meningitis which brought him to hospital. Only prompt treatment saved his life.

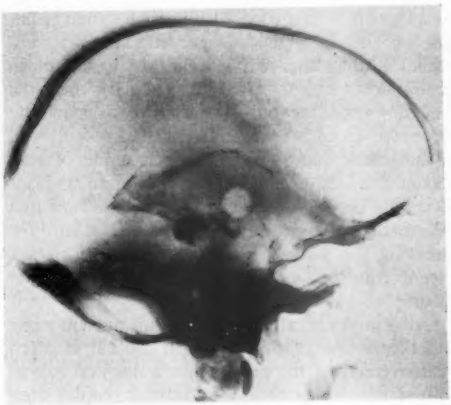

Fig 5 *A radiograph illustrating that Thorotrast has leaked from the abscess into the ventricle. The temporal burr-hole is also seen*

These figures illustrate that sinus thrombophlebitis and meningitis are now controllable by antibiotic therapy and that the main problem lies in the management of cerebral, cerebellar and subdural abscesses. These abscesses have often followed on, or been associated with, other intracranial lesions. Cerebral and cerebellar abscesses are preceded for at least three to four days by a thrombophlebitis, and subdural abscess usually occurs late in the illness. Therefore, if effective treatment is undertaken soon after the onset of an intracranial complication it should be possible to prevent the development of lethal lesions. The earlier the diagnosis, the better is the prognosis.

In most cases a diagnosis can be reached within the first forty-eight hours. Even if the lesion cannot be labelled accurately the suspicion that an intracranial lesion has occurred should provide sufficient knowledge to begin active therapy. What is merely suspicion is often confirmed later.

A meticulous chronological history of events is essential to accurate diagnosis (Table 3). The simple fact that the ear is producing symptoms or signs other than otological ones or even that the patient himself is unwell means that the suppuration has extended beyond the middle ear cleft. In chronic ear disease, earache alone means something has gone wrong and if pus is under pressure within the middle ear cleft an intracranial lesion may be impending. Headache and vomiting, the symptoms of raised intracranial pressure, indicate that an intracranial lesion has already started. A raised temperature with a chronic ear or late in the course of acute ear disease suggests a meningitis or sinus thrombosis; if the temperature swings or rigors develop then

Table 3

Early symptoms and signs of otogenic intracranial complications

Patient is unwell	
Earache	Epileptic fits
Headache	Nominal aphasia
Vomiting	Neck rigidity
Swinging temperature or rigors	Nystagmus
Drowsiness – coma	Temperature and pulse charts

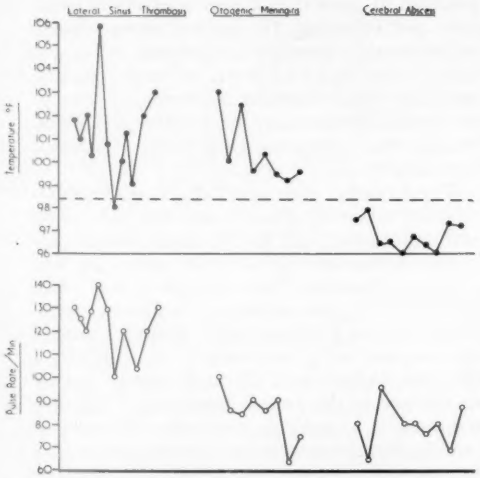

Fig 6 *Portions of temperature charts from three recent cases. The upper charts show temperature in degrees F and the lower chart pulse-rate per minute.*

the patient without doubt has a sinus thrombophlebitis. On the other hand when the temperature remains raised with a relatively slow pulse the patient probably has meningitis, or if the pulse-rate and temperature are subnormal a cerebral or cerebellar abscess has probably formed. Fig 6 illustrates these features from parts of the temperature charts of 3 recent patients. Slight drowsiness means that brain tissue is involved unless proved otherwise. Epileptic fits are certain evidence of cortical irritation and when they occur early probably signify the presence of a cerebral thrombophlebitis; but, if the fits are not controlled fairly quickly by adequate antibiotic therapy the patient should be regarded as having a subdural abscess. Nominal aphasia points to a lesion in the dominant hemisphere. However, the opposite temporosphenoidal lobe is silent and the diagnosis must be suspected on the general picture, and in a co-operative patient by testing the visual fields. Neck rigidity obviously means meningeal irritation but only the time of its development in the history will indicate whether this is a single lesion or a leaking abscess. Nystagmus suggests a labyrinthine erosion or a cerebellar lesion but it is only the accompanying findings which allow the clinician to see the sign in its correct perspective. Other physical signs are late in appearing in the natural history of the intracranial extension, although only a few days may have elapsed in the chronological history. Frequently a tender jugular vein and upper deep cervical nodes and occasionally a subperiosteal abscess over the parietal and occipital bones have been seen in sinus thrombosis. The extent of tenderness over the jugular vein is often a useful sign of the lowest level reached by the thrombophlebitis. A progressing hemiplegia indicates a large abscess in the brain or subdural space, and deep coma with fixed dilated pupils a gross supratentorial hydrocephalus. Papillœdema is usually a late sign, taking two to three weeks to develop in the case of cerebral abscess, but when papillœdema and a raised intracranial pressure appear early and are the only findings the patient probably has the so-called otitic hydrocephalus which in my opinion means no more than that the larger lateral or transverse sinus or the sagittal sinus has become thrombosed.

Lumbar puncture is a useful method of confirming a clinical diagnosis already suspected. Sinus thrombosis occasionally produces raised cerebrospinal fluid pressure, a frank meningitis is obvious enough but even a small number of cells in the fluid is not inconsistent with the presence of brain abscess. Tobey-Ayer and Queckenstedt tests are of no value, for positive or negative findings are not conclusive. When a patient has meningeal irritation, a smear of the cerebrospinal fluid should be examined to determine whether cocci or bacilli are present. If cocci are found, penicillin, streptomycin, or sulphonamides are indicated, whereas if bacilli, chloromycetin or sulphonamides should be used. When no organisms are found penicillin and streptomycin have been used. On two occasions Gram-negative cocci were found but these turned out to be degenerate Gram-positive cocci as determined by culture. To await positive culture of the cerebrospinal fluid or of blood culture in the case of sinus thrombosis before starting treatment is to court disaster.

Electroencephalography is useful when findings are positive, but is of doubtful value when negative at the first recording. Angiography, encephalography and ventriculography have a place in diagnosis but in my experience by the time they are used the patient has already partially recovered from a major intracranial lesion, and in fact most diagnoses have been made or suspected and active treatment undertaken without their aid. Testing of the visual fields and repeated electroencephalography are particularly useful for assessing the patient after he has made an apparent full recovery from a major intracranial lesion.

Unfortunately, all patients do not present early and the timing of operation on the ear is often controversial. If the patient has a marked supratentorial hydrocephalus or tonsillar coning then the cerebral or cerebellar abscess requires urgent treatment and the ear must take second place. In a temporal lobe abscess, a temporal burr is the most direct approach and should be within the

compass of the otolaryngologist. This approach is through a clean field and also avoids the development of cerebral herniation. A cerebellar abscess is usually situated in the antero-superior part of the lobe and I think that the direct approach through Trautmann's triangle or the lateral sinus is as good as, if not better than, the suboccipital approach – a suboccipital tap in the hands of the inexperienced is more likely to miss the abscess. The majority of the recoveries in cerebellar abscess in this small series were obtained by transmastoid tapping. A limited inspection of the middle and posterior fossæ by the neurosurgeon through a burr hole, although important, cannot deal with the ear and the associated extradural disease or sinus thrombosis.

The ear itself is very important, for it is the source of the infection and in uncontrolled acute and chronic ear disease surgical exploration is essential. A persistent nidus for bacteria, such as cholesteatoma, is untouched by antibiotics and the early removal of this source eliminates the possibility of recurrent infection of the intracranial tissue planes and frequently shortens the length of the illness. The bacteria causing the intracranial lesions are most commonly a pyococcus, occasionally *H. influenzæ*, *B. coli* or *pyocyaneus*. I therefore always treat these infections primarily with penicillin and streptomycin or sulphonamides and within forty-eight hours explore the ear if advisable. Dramatic improvement has frequently followed the removal of the septic focus. Time prevents my quoting many of the numerous instances when a patient who is deteriorating or whose lesion has relapsed on antibiotic treatment alone, improves within a few hours after the operation. At operation, the lateral sinus and middle fossa dura are deliberately exposed even if not thought to be involved, for frequently a middle fossa extradural abscess is associated with a lateral sinus thrombosis and many cases of temporal lobe abscess were associated with lateral sinus and superior petrosal sinus thrombosis. Ideally, all otogenic intracranial lesions should be managed in a hospital where an otologist and a neurosurgeon are readily available and work in co-operation. The post-operative care is not easy and frequent examination and careful assessment by skilled clinicians, senior and junior alike, are essential to the well-being of the patient.

Acknowledgments: I would like to thank Mr F McGuckin and Mr Munro Black for allowing me to include the cases admitted under their care and also permitting me to treat many of them during the last seven years. Mr D J Hammersley of the Department of Surgery kindly drew the histograms.

Mr J Angell James (*Bristol*) said that he was impressed by the large number of cases of intracranial complication of otogenic origin which Mr Dawes had collected from the Royal Victoria Infirmary. Did these numbers include all the cases seen in the neurosurgical unit also? In the E.N.T. Department of the United Bristol Hospitals the number was much smaller. He had looked up the number seen in six years, from 1929 to 1935 inclusive, and compared it with the number seen from 1954 to 1959 inclusive. In the presulphonamide period there were 56, and in the last six years only 17, the total number of beds in the Department being 60. He thought the experience in Newcastle must be exceptional. In view of the small number of intracranial complications seen in the average E.N.T. clinic he thought it was important that registrars in training should be encouraged to spend time in either a neurosurgical or neurological unit in order to gather enough experience of these very important problems. He particularly welcomed Mr Pennybacker's suggestion for the first-aid treatment with urea for cases in bad condition in preparation for transport to a distant neurosurgical unit. In the South West Region this type of case might have to travel 200 miles.

Mr J W Dixon (*Glasgow*) wondered how urgent we should regard the common case of chronic otitis media with cholesteatoma and foul discharge, but without any symptoms or signs of intracranial extension. Though very few of these might subsequently develop intracranial complications, some of those that did so still lost their lives even in the antibiotic era. Perhaps these cases should be dealt with as semi-emergencies even if this meant that there was only time to render the ear safe and that possibly tympanoplasty would have to be left for a second-stage operation later.

He was prompted to say this by the case of a young man who developed symptoms of intracranial extension after a short period on the waiting list. Though then admitted immediately and treated with neurosurgical advice right from the start, the patient subsequently died.

Mr J Fulton Christie (*Glasgow*) said the question of timing of the mastoid operation in these cases was important, although not vital. He was old enough to remember the pre-antibiotic days when the first step was to operate on the diseased mastoid. When antibiotics became available and the neurosurgical unit was established in the West of Scotland the intracranial complication, the condition dangerous to life, was naturally dealt with first. The pendulum probably swung too far in the opposite direction and the mastoid operation was often delayed until the meningitis or brain

abscess had been cleared up, and sometimes even until an abscess capsule had been excised. His view at present was that in the first place the infection should be controlled by antibiotics and the intracranial pressure reduced where necessary, by abscess tap, &c. The mastoid operation should then be done as soon as the patient was in a fit condition for the administration of a general anæsthetic.

He was pleased to hear Mr Pennybacker advise ventriculography as he (Fulton Christie) thought that every patient who had been treated for brain abscess or meningitis ought to have a ventriculogram before being dismissed from hospital. He knew of some cases where this had been omitted because the patient appeared to be so well, and the patient had to be readmitted within a very short time, as a second abscess or small loculus had been overlooked and had flared up.

He was surprised that the question of a dead labyrinth had not been mentioned, he wondered what Members' views were on this. Personally he believed that whenever a dead labyrinth was found it should be opened freely above and below the facial nerve.

Mr J D K Dawes, in reply to Mr Angell James, said that 14 intracranial complications of ear disease had been admitted in 1960. The mortality rate was high because many patients were not seen by the otologist or neurosurgeon, and many others arrived for treatment in a moribund state. In defence of transmastoid tapping of a cerebellar abscess, Mr Dawes did not advocate this in the hands of the neurosurgeon but only as a familiar approach to the otologist in an emergency. The 2 cases of cerebellar fungus shown by Mr. Pennybacker appeared to have had a cerebellar exposure posterolateral to the lateral sinus and the dural opening was excessive. Mr Dawes had never seen a cerebellar fungus result from cerebellar tapping through Trautmann's triangle. Although only the major intracranial lesions had been considered, 2 cases of subarachnoid cyst occurred in the series; both settled satisfactorily with tapping by a brain cannula.

Giving due consideration to Mr McGuckin's recent Annual Address at the Institute of Otology (1960, unpublished) on the subject of chronic ear disease and keratosis, Mr Dawes suggested to Mr Dixon that it was essential to examine the ear carefully under a microscope and to discuss fully the indications for surgery with the patient. The hearing might be preserved or improved; a dry ear might be obtained, and there was an excellent chance of preventing the development of an intracranial lesion at a later date. Since his waiting list for an endaural mastoidectomy was almost eighteen months, all patients with potentially dangerous ears were kept under observation in the outpatient department during the waiting period. Even so, the general practitioner must still be responsible for recognizing the emergency between visits.

Penicillin had been used intramuscularly, in a dose of 1,000,000 units six-hourly, and intrathecally in cases of meningitis and brain abscess in a dosage of 5,000 to 10,000 units. The only catastrophe he had seen was due to the accidental injection of 5,000,000 units intrathecally. Mr Dawes had never needed to tie an internal jugular vein for sinus thrombosis, and had not interfered with a solid or mural clot, opening the sinus only when its wall was necrotic or when the lumen contained pus.

He agreed that the killing lesion should be treated first. The labyrinth had only on two occasions been suspected as a cause of intracranial invasion in this series, and as a rule he had dealt with the labyrinth on its own merits.

Section of Physical Medicine

President R W Windle MD

Meeting December 14 1960

Discussion on Electrodiagnosis

Dr B G B Christie (*London*)

Electrodiagnostic Features of Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease is a degenerative disease of the anterior horn cells of the spinal cord, with a slight predominance in the male sex. Cases may present in childhood, early adult life or in the fifth decade. A family history is obtained in about 40% of cases.

Electrodiagnostically the earliest detectable change in the peripheral muscles is that commonly associated with lesions of the anterior horn cells of the spinal cord. On stimulation of the nerve trunks in the limbs the response to electrical stimulation is greater than the response of which the patient is capable on volition. The explanation of this phenomenon may be an apraxia of the anterior horn cells which are probably no longer under the influence of their central connexions.

On direct stimulation of muscle one is constantly impressed by the sharpness of the end-point of the response. In normal muscle, with diminishing stimuli above the rheobase the response gradually diminishes, whereas in lesions of the anterior horn cells such as amyotrophic lateral sclerosis and Charcot-Marie-Tooth disease, there is a full response at a point immediately above the rheobase, but when this point is reached there is an immediate all-or-none response. The probable explanation of this finding is the larger territory of the motor unit found in neurogenic atrophy of central origin.

On needle electromyography of the muscles one is first concerned with the spontaneous activity at rest. In Charcot-Marie-Tooth disease these findings depend on the muscle examined and the stage of the disease in that particular muscle. In clinically overt cases one expects to find monophasic or diphasic denervation potentials, that is positive potentials or fibrillation in about 40%. In more advanced cases where marked wasting is present in the peripheral muscles it is common to find no spontaneous activity, reflecting the fact that no reactive tissue is present. These findings hold for the small muscles of the foot, and to a lesser extent for the small muscles of the hand for reasons that I shall discuss later. If the tibial or forearm muscles are examined the findings differ from those of the small muscles of the hand and foot. In a muscle such as tibialis anticus it is the rule to find denervation potentials in more than 75% of cases, and in my own series high frequency myotonic discharges were found in 15% (Christie 1959). I have only found these discharges in tibialis anticus in Charcot-Marie-Tooth disease, and I have never seen them in the upper limb. Myotonic discharges are not uncommon in states of denervation and have previously been described in these conditions by Worster-Drought & Sargent (1952).

Examination of the proximal muscles of the lower limb such as vastus medialis shows that denervation potentials are almost never seen, and on direct stimulation of the muscle evidence of denervation is wanting in the majority of cases. This is in contradistinction to the original findings of Charcot & Marie (1886) who stated '. . . the thigh muscles appear to retain their volume and power, although, as we shall see from the electrical examination this integrity is more often apparent than real'.

When muscles are examined with a concentric needle electrode the findings on minimal volition depend on the muscle selected. In the most distal muscles of the limb marked denervation is the rule in established cases, the pattern usually being one of single oscillations, and in the small muscles of the hand and foot the amplitude of these oscillations is usually in excess of 5·0 mV; the amplitude of the interference pattern on volition is always larger in these sites than in other muscles in the body. In consequence it is erroneous to attach any importance to the amplitude of the oscillations in these particular muscles. In the tibial muscles the findings on minimal volition are similar to those found in the distal muscles, namely single oscillations of large amplitude, but in this site oscillations of 5·0 mV in amplitude strongly suggest a

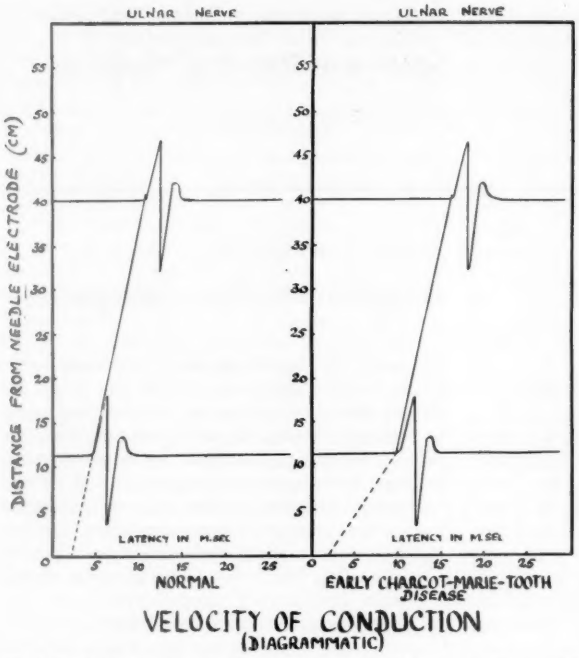

Fig 1 *Early changes in velocity of conduction and latency in Charcot-Marie-Tooth disease*

lesion in the anterior horn cells of the spinal cord. In the thigh muscles similar findings are observed. As volition increases from minimal to maximal it can be seen that the amplitude of the pattern decreases, i.e. there is an inversion of recruitment. This is contrary to the normal finding where, with increasing effort, there is an increase in the amplitude of the interference pattern. On maximum volition there is a qualitative decrease in the interference pattern which is usually of the single oscillation type and at the most a mixed pattern.

Velocity of conduction measurements along the lateral popliteal nerve in the lower limb and the ulnar nerve in the upper limb show that slowing is the rule, and that in some cases it may be very marked. The average velocity of conduction along the lateral popliteal nerve in Charcot-Marie-Tooth disease was 42·8 metres per second (m/s) in 23 cases, whereas the average normal was 47·1 m/s (Christie & Coomes 1960). Pick-up was by a concentric needle electrode in extensor digitorum brevis. Along the ulnar nerve to the first dorsal interosseous the normal average was 56·7 m/s whereas in Charcot-Marie-Tooth disease the average velocity was 36·2 m/s in 36 cases. It may appear discrepant that the average velocity in this condition is nearer the normal mean in the leg than the arm. This is because in the leg in a number of advanced cases it was not possible to make a recording from the peripheral muscles, whereas I have never failed to record the velocity of conduction to the first dorsal interosseous.

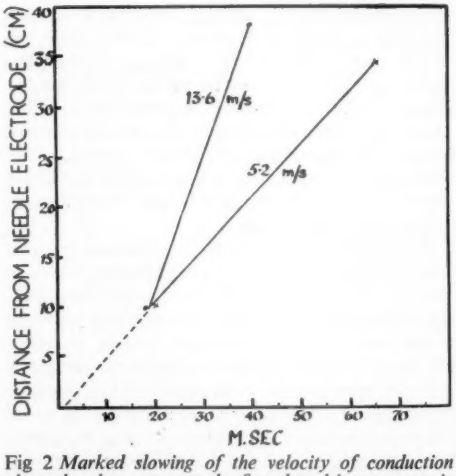

Fig 2 *Marked slowing of the velocity of conduction along the ulnar nerve to the first dorsal interosseous in two patients with Charcot-Marie-Tooth disease*

In Fig 1 it may be seen that latencies at say the elbow and wrist are more important than the time taken for the impulse to pass between these two points. Velocity of conduction may remain largely unimpaired while the increased latency at the elbow and wrist shows that the greater part of the delay occurs in the most terminal part of the nerve distal to the distal point of stimulation. This obtains only in cases of moderate involvement. When the disease has progressed to a greater extent velocity of conduction becomes markedly slowed, and Fig 2 shows graphs of the velocity of conduction along the ulnar nerve to the first dorsal interosseous in two patients whose velocities were 5·2 and 13·6 m/s respectively. In an attempt to explain these phenomena Bauwens (1959) has postulated that in pathological states of peripheral nerves there exist two conditions that he has named axonostenosis and axonocachexia. In axonostenosis there is a localized narrowing of the axon that may affect one fibre more than another, and as velocity depends *inter alia* on the diameter of the axon there will be localized slowing of conduction through the stenotic area affecting some fibres more than others and temporal dispersion of the recorded response. When stimulation takes place below this stenosis there will be no such dispersion.

Axonocachexia may result from a more proximal stenosis and implies that the narrowing of the axon at the level of the stenosis is continued distally along the axon to the neuromuscular junction. When these conditions prevail there is slowing of the impulse not only at the site of the stenosis but throughout the length of the nerve fibre distal to this site. A further feature of axonocachexia as pointed out by Bauwens is that the threshold is considerably raised in the attenuated fibres, and they may be impossible to stimulate.

In Charcot-Marie-Tooth disease the findings in the earliest stages are those of neurogenic atrophy of central origin, but as the disease progresses the findings become a combination of central and peripheral neurogenic atrophy. Changes in the velocity of conduction (Fig 3) which by serial examination I have shown to become retarded as the disease progresses can be explained by a gradually progressive axonocachexia starting at the peri-

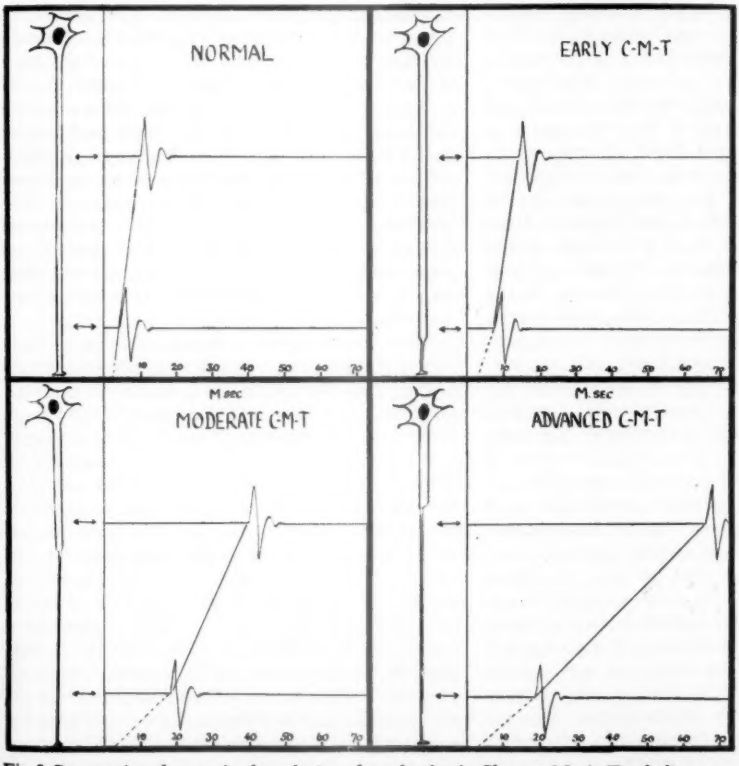

Fig 3 *Progressive changes in the velocity of conduction in Charcot-Marie-Tooth disease*

phery and slowly moving more proximally, leaving in its wake distal axonotmesis. This is evident when distal muscles become totally denervated and it is no longer possible to stimulate them through their nerve of supply, but histological studies carried out by Coërs & Woolf (1959) have shown that reinnervation of the previously denervated units occurs by branching of the existing neurons. Temporal dispersion of the recorded phenomenon is not a feature of this disease, and in more than twenty cases the duration of the recorded response was within normal limits. I have had the opportunity to examine only one patient suffering from this disease with a multielectrode, but in this case I was impressed with the large territory of the motor unit.

Clinically a curious feature of the disease is the peripheral onset with proximal progression, the transverse involvement of the muscles in the limb and the later involvement of the upper limb with atrophy starting peripherally and progressing proximally, but never to such a great extent as in the lower limb. Weiss (1956), in a description of the life history of the neuron, has described the proximo-distal flow of axoplasm from the anterior horn cell along the axon to the periphery. Failure of the neuronal pump causes failure of the most distal axonal ramifications, resulting initially in axonostenosis and later complete denervation. The longest axons in the body are those to the small muscles of the sole of the foot, and it is here that Charcot-Marie-Tooth disease starts. Because failure of the intrinsic muscles of the feet causes little disability the disease may not be detected at this stage, but I have found evidence of neurogenic atrophy of central origin in the small muscles of the foot in symptomless siblings of patients suffering from overt disease. In the hereditary form of the disease there appears to be a failure of the anterior horn cell to pump axoplasm to the periphery. An interesting observation is that muscles at equal distances from the spinal cord are affected at approximately the same time, and the incidence of atrophy in the small hand muscles occurs at about the same time as the calf muscles show evidence of denervation. By surface measurement these two groups are equidistant from the spinal cord. By this same reasoning wasting and signs of denervation are most uncommon in the proximal parts of the upper limb. A clinical syndrome in all respects similar to Charcot-Marie-Tooth disease occurs in elderly persons, and the electrodiagnostic findings are identical. In these patients the upper limbs are not usually involved owing to the late age of onset and the slow progression of the disease. It is my hypothesis that this may be caused by a failure of the anterior horn cell due to senility.

In conclusion I may summarize the findings in Charcot-Marie-Tooth disease in the established case as those of complete or marked denervation in the peripheral muscles of the limb, with more proximal muscles such as those of the tibial region showing a mixed picture of neurogenic atrophy of both central and peripheral origin, whereas the still more proximal muscles such as the thigh muscles show an uncomplicated picture of neurogenic atrophy of central origin. Similar findings in the upper limb occur at a later date. I postulate that the cause of the disease may be a failure of the anterior horn cell to pump axoplasm to the periphery with resulting denervation.

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Dr R W Gilliatt (*London*)

Sensory Nerve Conduction in Man

Electrical investigation of the sensory system is only a small part of electrodiagnosis but it is one in which several recent advances have occurred. We can now record activity directly from human peripheral nerves in both the arm and the leg; alternatively, we can stimulate peripheral nerves in the limbs and record the arrival of the afferent volley in the sensory cortex. These techniques have reached the stage of having some practical clinical value and I should like to review them briefly. In this type of work technique is all-important, and it seems to me that this whole field of electrodiagnosis only remains viable if we continually modify our procedures and add new ones to broaden our understanding of peripheral nerve function.

Three years ago at a meeting of this Section concerned with nerve pressure syndromes (*Proceedings*, **51**, 87) I discussed a method of examining conduction in sensory nerves which had been developed by Dawson (Dawson & Scott 1949, Dawson 1956), and which could be applied to patients with peripheral nerve lesions affecting the upper limb. At that time there was no comparable method of examining sensory conduction in the lower limbs. Dawson's technique for the upper limb is now well known and I will only mention it briefly. It involves electrical stimulation of a peripheral nerve in order to produce a volley of afferent impulses; this ascending volley can then be detected by surface electrodes placed over the nerve trunk at a higher level in the arm. The essential part of the procedure is to produce a synchronous volley as spontaneous activity occurring asynchronously in different fibres can-

not be detected with surface recording. Even with synchronous volleys, nerve action potentials are often very small, and in order to distinguish them from random fluctuations of the trace we usually superimpose a number of responses on the same piece of film. The stimulus is set to repeat at a convenient rate such as once per second, and the camera shutter is left open so that 50 or 100 successive traces on the oscilloscope are photographed.

For clinical purposes three standard positions of stimulating and recording electrodes have been used. First of all, stimulation of the finger with recording at the wrist; in this way purely sensory action potentials are recorded (Gilliatt & Sears 1958). However, when we stimulate the nerve trunk at the wrist with recording electrodes above the elbow, we record antidromic impulses in motor fibres as well as impulses in sensory fibres, so that at this level we are concerned with a mixed nerve volley. The same applies to the third position in which the electrical stimulus is put into the nerve just above the elbow and the action potential of the ascending volley recorded in the axilla (Gilliatt & Thomas 1960).

All this is well established, and what we have been more concerned with recently has been to extend the technique in order to record action potentials from the lateral popliteal nerve in the leg (Gilliatt *et al.* 1961). For this purpose we stimulate the anterior tibial nerve on the dorsum of the ankle and record the action potential of the ascending volley as it passes up the lateral popliteal nerve at the head of the fibula. At first we used surface recording electrodes of the type developed by Dawson & Scott for the arm, but later tried small steel needles inserted through the skin so that they lay at right angles to the nerve trunk; this resulted in a substantial increase in the size of the recorded potential. We do not attempt to transfix the nerve with the needle tip but simply place the electrode under the skin within a few millimetres of the nerve trunk. We now use this type of needle electrode almost universally in the leg in preference to surface recording.

The anterior tibial nerve contains motor fibres to extensor digitorum brevis as well as sensory fibres from the dorsum of the foot, so that the nerve action potential is derived not only from orthodromic impulses in sensory fibres but also from antidromic impulses in motor fibres. One way of distinguishing between the two is to examine patients with motor neuron disease in whom muscle wasting in the legs is so severe that only the sensory fibres remain, all the motor fibres having been eliminated by the disease. In such cases small but well-formed nerve action potentials can still be recorded from the lateral popliteal nerve at the head of the fibula; here one can say with confidence that the potentials are derived entirely from sensory fibres in the nerve trunk. It is clear, therefore, that sensory fibres alone are present in the anterior tibial nerve in sufficient numbers to produce a recordable potential even when all the motor fibres have disappeared. Thus if, in pathological cases, we see a completely flat trace, it is justifiable to conclude that the disease is affecting both motor and sensory fibres. A flat trace due to complete loss of the action potential has in fact been the usual finding in patients with peripheral neuritis. This has been so in relatively mild cases as well as in severe ones, and we have found it of some practical value in confirming the presence of damage to the peripheral part of the sensory system.

Another new technique which has obvious application to clinical problems has been developed by my colleague Mr T A Sears, at the National Hospital, and I am grateful to him for allowing me to refer to it. What Sears has done has been to get away from the technique of electrical stimulation and to develop a method of recording from sensory nerves during natural stimulation of their end-organs. A sharp tap on the nail of the index finger is used as the natural physiological stimulus (Sears 1959). This also triggers the sweep of the oscilloscope and when one records from the median nerve at the wrist there appears, 4 or 5 milliseconds after the mechanical stimulus, a small sensory action potential about 5 microvolts in amplitude. This is not a very large potential, and Sears then took things a step further by tapping the nail and recording from the digital fibres in the finger itself. This provides a simple and painless method of examining mechanoreceptors in the finger and their afferent fibres, and it is already providing interesting information about sensory nerve function in disease (Bannister & Sears, to be published).

Finally, I wish to refer to work that has been going on at the National Hospital concerned with the recording of evoked potentials from the sensory cortex through the intact skull in man (Dawson 1954, Giblin 1960). From animal work it is well known that when a peripheral nerve is stimulated, an evoked potential can be recorded from the surface of the contralateral cerebral hemisphere. In man, however, when evoked cortical potentials are recorded through the intact skull and scalp, their amplitude is much less than that of random cerebral activity, and in order to record them at all this random activity must be rejected. For this purpose an electromechanical storage unit was specially developed by Dawson (1954). This device is able to store successive traces so that after 100 or 200 repetitions of the stimulus it presents an averaged record from which random activity has disappeared, and in

which the cerebral response to a peripheral stimulus can be clearly seen.

Using the storage unit, Giblin (1960) has recently recorded evoked potentials from the sensory cortex through the scalp in a large number of healthy subjects, the peripheral stimulus being applied to nerve trunks in either the arm or the leg. As might be expected, evoked potentials have been reduced or absent when the peripheral nerve stimulated has been damaged by a localized lesion or by a generalized peripheral neuritis. Giblin also found that lesions of the posterior roots or of the posterior columns of the spinal cord prevented the afferent volley from reaching the sensory cortex, whereas lesions of the spinothalamic tracts were without this effect. The technique may thus be used to confirm the presence of a certain type of spinal cord lesion, and in conjunction with the tests of peripheral nerve function described previously, it can be of considerable practical value in electrodiagnosis.

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Dr A L Woolf (*Smethwick*) said that since 1929 when Adrian & Bronk first recorded motor unit action potentials by means of concentric needle electrodes, much empirical information had been obtained through the study of diseased muscles by such electrodes. During the same time much relevant knowledge had also been gleaned from other fields of investigation, and especially through the use of intracellular electrodes (Graham & Gerard 1946), the introduction of multilead electrodes by Buchthal (1957) and his collaborators and vital staining of nerve endings and histochemical demonstration of cholinesterase in muscle biopsy specimens by Coërs (Coërs 1952, 1953, Coërs & Woolf 1960). The fruits of these studies should now be integrated in the general theory of electromyography. The relationships between the motor unit action potentials of clinical electromyography and the single fibre action potentials recorded by intracellular electrodes on the one hand, and the axonal sprouting observed in vitally stained preparations on the other, were important in explaining and interpreting electromyograms. Sprouting was also important in interpreting the changes in motor unit territories reported by Buchthal and his collaborators. The quite special changes seen in the terminal motor innervation in dystrophia myotonica were of particular interest in their association with the high frequency discharges characteristic of this condition. Knowledge of the structural arrangement of the intramuscular nerve bundles and endings and their alteration in disease was particularly valuable in understanding how quite similar electromyographic findings ('distal neuronitis') could be obtained in such different diseases as motor neuron disease, myositis and peripheral neuritis (Bauwens, 1954, 1955, 1959).

[A fuller account of this paper will appear elsewhere.]

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Section of Pædiatrics

President B E Schlesinger OBE FRCP

Meeting October 28 1960

Cases

Secreting Intrathoracic Ganglioneuroma

Jean M Smellie MRCP DCH & M Sandler MRCP
(for Bernard Schlesinger FRCP)

M A, female, born 24.1.58.
Greek Cypriot transferred from Nicosia Hospital to care of Dr Bernard Schlesinger.

Dr Smellie

History: Intractable diarrhœa with failure to thrive for eighteen months. No respiratory symptoms, but large opacity in right hemithorax discovered on X-ray. Transferred for investigation and removal of tumour, aged 2 years 7 months.

On examination: Fretful, wasted child with marked gaseous abdominal distension. Profuse sweating and considerable thirst. Brassy cough. No stridor. Fullness of right upper chest with impaired movement, dull percussion note and absent breath sounds anteriorly and posteriorly. Mediastinum displaced to left. Persistent hypertension with blood pressure 150/110 to 260/150. No abnormal neurological signs.

Investigations: Urine: routine normal. X-rays of chest: uniformly dense opacity right hemithorax (Fig 1). Deformity right 3rd rib. Abdomen: multiple fluid levels in distended gut – corrected following potassium administration. I.V.P.: normal. Skeleton: no metastases. Plasma K^+ 2·8 rising to 5 mEq/l. following oral KCl. Plasma Na^+, HCO_3^- and Cl^- within normal limits. Blood urea normal. Fasting blood sugar 78 mg/100 ml. Hormone assays: Considerable excess of dopamine and noradrenaline found in urine. Phentolamine test inconclusive.

Thoracotomy Miss Doreen Nightingale (1.9.60): Smooth lobulated extrapleural tumour with intercostal extensions completely removed after separation from wide area of fusion to posterior thoracic wall. Blood pressure was controlled with phentolamine, but little variation occurred with handling or clamping of blood supply to tumour.

Progress: Blood pressure fell to normal levels over ten days and has remained normal (85/45) (Fig 2). Normal stools post-operatively. Abdominal distension decreased.

9.9.60 (eighth post-operative day): No excess of urinary pressor amines detected.

Pathology and chemistry of tumour: Ganglioneuroma, with uniform cut surface, weight 270 g. Noradrenaline, dopamine and dopa isolated from tumour. No evidence of chromaffin reaction to bichromate.

Discussion: There are at least 5 reported cases in childhood of neuroblastoma associated with persistent or paroxysmal hypertension and excessive

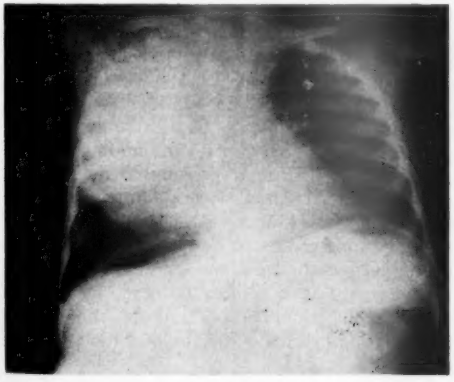

Fig 1 *Pre-operative X-ray of chest*

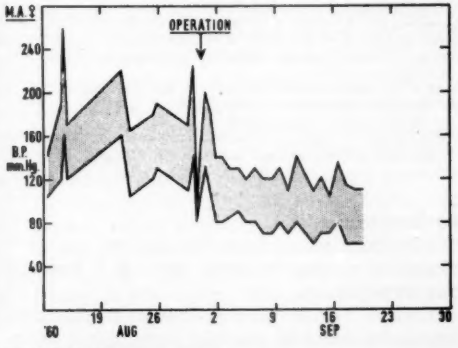

Fig 2 *Blood pressure record*

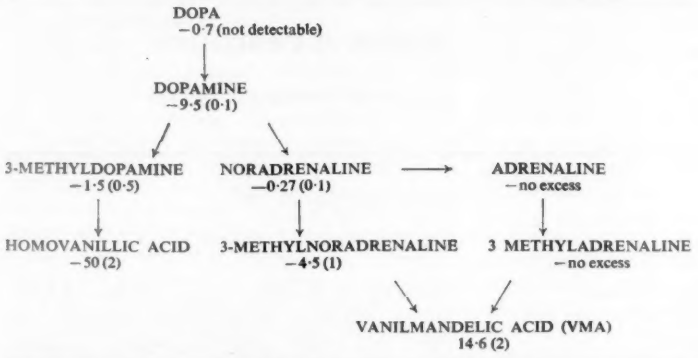

Fig 3 *Showing schematic pathway of dopa metabolism with representative assay figures of various metabolites (mg/24 h) in urine from this patient. Approximate normal values for children of this age are given in brackets*

urinary catecholamines. No diarrhœa occurred in these and abdominal distension was not a feature (Mason *et al.* 1957, Isaacs *et al.* 1959, Wilkins 1957).

Also, 5 cases have been recorded (Green *et al.* 1959, Stickler *et al.* 1959, Greenberg & Gardner 1959) of the occurrence of diarrhœa, wasting and abdominal distension, associated with ganglioneuroma in 3 cases and ganglioneuroblastoma in 2 cases. 4 of these children were hypertensive, and where catecholamines were sought, they were excreted in excess. All 5 children were under the age of 3 years. Where the tumour was operable, abatement of symptoms and normal blood pressure followed its removal.

Diarrhœa is not a feature of phæochromocytoma (Smid & DuShane 1955) and did not occur in the first 5 children with secreting neuroblastoma mentioned above. This suggests that the tumour might possibly secrete a further metabolite responsible for the alimentary symptoms.

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Dr Sandler
The biochemical studies on this patient were performed in conjunction with Mr C R J Ruthven and Dr S E Smith.

Typical urinary twenty-four-hour excretion figures for catechols and their metabolites, representative of many examinations, are shown in Fig 3, which presents a schematic pathway of dopa metabolism.

All values returned to normal after the tumour which contained dopa, dopamine and noradrenaline had been resected.

Although 5 cases of this clinical syndrome are described in the literature, it had not been previously suspected that the catecholamine secretion pattern was different from that found in phæochromocytoma in which noradrenaline, a greater or lesser amount of adrenaline, their 3-methoxylated metabolites and vanilmandelic acid (VMA) are found in the urine in excess (Sjoerdsma *et al.* 1959). Though these compounds were present in excess in this patient, comparatively enormous quantities of dopamine and its major metabolite, homovanillic acid, were also in evidence. Whilst similar biochemical findings have been recorded (for references *see* von Studnitz 1960), this is the first time that they have been shown to correlate with the clinical picture described here.

These large amounts of unchanged dopamine in the urine may well have derived to a great extent from direct renal decarboxylation of dopa (Holtz *et al.* 1942) which was identified both in urine and tumour tissue. The excretion pattern may thus be analogous with the finding of large amounts of 5-hydroxytryptamine in the urine of patients with 5-hydroxytryptophan secreting carcinoid syndrome (Sandler & Snow 1958). Most of the dopamine produced by the tumour itself was probably metabolized and represented in the urine largely as homovanillic acid, just as the vastly greater proportion of noradrenaline from a phæochromocytoma is metabolized before excretion.

No direct enzyme studies were performed; however, the finding of noradrenaline in tumour tissue,

presumably responsible for the hypertension, indicates that some dopamine-β-hydroxylase activity was present. Dopamine and noradrenaline similarly attest to the presence of dopa decarboxylase.

Although it is tempting to suggest that the diarrhœa in this syndrome is caused by dopamine, there is little evidence at present to support this view. Large amounts of an unknown catecholamine, detected chromatographically, in urine extracts from our patient, might equally well be the cause. No excess of 5-hydroxyindole acetic acid, the major metabolite of 5-hydroxytryptamine, was detected in the urine.

This case will be published in full elsewhere.

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Congenital Tracheo-œsophageal Fistula

Leonard Haas MD MRCP & M F Sturridge FRCS (for N M Jacoby MD FRCP & T Holmes Sellors MCh FRCS)

H M, male, aged 9 years, Turkish Cypriot.

History: Youngest of 4 children. History was difficult to obtain owing to language difficulties. The patient has 'always' had a cough, sometimes associated with wheezing. This cough became worse one month prior to admission.

On admission: Temperature 98·4°F, pulse 62, respirations 20. Numerous coarse and fine râles and prolonged expiratory sonorous rhonchi widely distributed over both lung fields.

Investigations: X-ray chest – Diffuse mottled pulmonary infiltration suggesting a coarse miliary pattern. Enlarged hilar glands. Mantoux 1:1,000 negative on 3 occasions. Blood count: Hb 87%, W.B.C. 4,000 (polys. 24%, lymphos. 70%). E.S.R. 19 mm in one hour.

Progress: His cough improved, the physical signs in the chest regressed until only a few scattered expiratory high-pitched rhonchi were audible. He gained 15 lb in the course of four weeks. There was no significant change in the X-ray appearance of the chest. Following discharge his clinical condition deteriorated, and after one month he was again admitted to hospital. X-ray of the chest showed no material change in the lungs, but the presence of air in the œsophagus seen on several films taken on different occasions was pointed out by Dr B C H Ward. Barium swallow: Movement of the barium was inco-ordinated and both obstruction and reflux were present at the distal end of the œsophagus. In both supine and erect positions fluid appeared to be in almost constant contact with the vocal cords and aspiration occurred. Bronchoscopy: A small opening 1–2 mm in diameter was seen just to the right of the mid-line in the posterior wall of the trachea. Œsophagoscopy: The upper œsophagus was 'roomy'. The mucosa was normal and no opening was seen. The œsophagoscope passed without obstruction into the stomach.

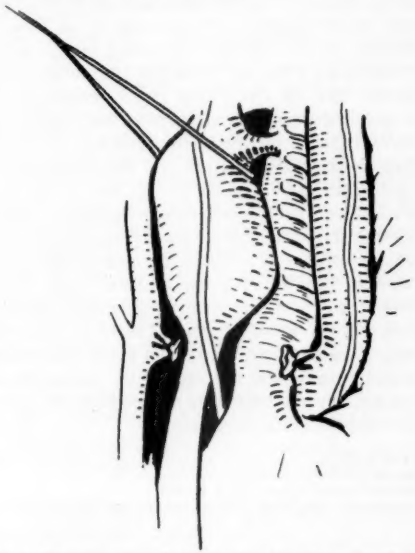

Fig 1 *Diagram to illustrate the junction of dilated œsophagus with the normal size lower segment. The high position of the fistula is also shown. The azygos arch is shown divided*

Operation: Left lateral position. Right thoracotomy via the upper border of the 4th rib. Findings: The œsophagus was dilated down to the level of the azygos vein below which it was of normal diameter. The azygos arch was divided to allow a full view of the œsophagus. The upper segment of the œsophagus joined the lower segment smoothly and without palpable thickening. Dissection between the œsophagus and trachea revealed a fistulous connexion about 5 mm in external diameter at the level of the neck of the 2nd rib (Fig 1). As it lay naturally, there was no length to the fistula and its walls blended smoothly with the posterior wall of the trachea. There were no adhesions in the vicinity to suggest a traumatic or inflammatory origin of the fistula. A No. 25 thread ligature was placed around the fistula close to the trachea and the œsophagus divided from the stump. The defect in the œsophagus was closed in two layers. The post-operative course was uneventful.

Comment: The interesting features of this case are the long survival without diagnosis, the apparently

infrequent attacks of severe respiratory infection and the dilatation and neuromuscular inco-ordination of the upper œsophagus. The rarity of respiratory infections may be explained by the narrow fistula and its high level which enabled the child to clear œsophageal contents from the trachea by coughing before they reached the lower airways. The dilatation and inco-ordination may be attributed to the passage of air from the trachea to the œsophagus during coughing and phonation. This air probably stimulated peristalsis, but, as there was no distension of the stomach, does not appear to have been swallowed. Its constant presence in the œsophagus presumably caused the dilatation and this, together with automatic regurgitation of air, led to the inco-ordination of the swallowing mechanism. Only 3 comparable cases have been found in the literature (Imperatori 1939, Haight 1948, Scott Dunbar 1958). All these children had feeding difficulties, vomiting and recurrent attacks of pneumonia from birth. Tracheo-œsophageal fistula was demonstrated either bronchoscopically or radiologically at the ages of $6\frac{1}{2}$, 4 and $3\frac{1}{2}$ years respectively and they were all operated on successfully shortly after diagnosis.

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T Substance Anomaly with Horseshoe Kidney

H M T Coles MD MRCP

N M, female, aged 2 years 10 months, was born spontaneously 5 to 6 weeks prematurely, weighing 5 lb 4 oz. Her parents and four older brothers and sisters are well. Always a slow feeder; since 2 months of age she has had persistent irregular vomiting. During her first admission to Westminster Children's Hospital when 1 year old she was found to have intermittent sterile pyuria in association with a horseshoe kidney. The pyuria has not been observed subsequently and her renal function is normal. The vomiting has continued, though is less frequent, and no alimentary cause has been found for this symptom. Her growth and nutrition are adequate: weight 24 lb 4 oz, height 33 in. (crown–pubis 19 in., pubis–heel 14 in.), span 31 in., head circumference $18\frac{7}{8}$ in. Severe mental retardation; no sphincter control; no speech. No evidence of deafness. EEG demonstrates a diffuse abnormality without clear focal or definite paroxysmal features. During her present readmission to hospital she has been found to pass T substance in her urine and this is believed to be significant in relation to the ætiology of her mental deficiency.

T substance was first detected in the urine of a

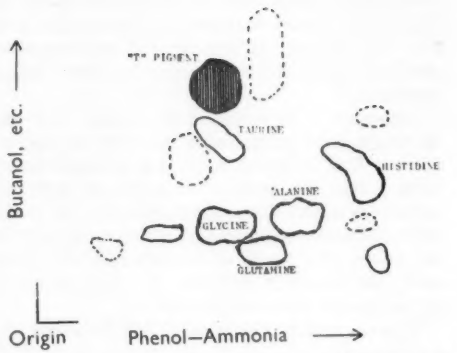

Fig 1 *Drawing of chromatogram showing position of T pigment spot.* (*Reproduced from Coles* et al. *1960, by kind permission*)

physically and mentally grossly retarded 4-year-old boy called Tony T in April 1959 and has been given the provisional name of T substance. When chromatography of his urine was carried out by the method of Bowden (1959) an unusual pigment was found near to the position of taurine (Fig 1). The spot appeared spontaneously during development in phenol-ammonia only after the urine had been previously desalted electrolytically and it continued to be detected when the patient was on a normal ward diet, free from sweets and other dye sources. It was not found in chromatograms of other, mentally normal, patients on the same diet in the hospital at that time (Wilkinson 1960).

The pigment, when eluted from the paper, left a pale pink residue after evaporation and this became reddish-purple when exposed to ammonia, in much the same way as murexide. This observation suggested that the anomaly might be due to a disorder of purine metabolism, and chromatograms indistinguishable by eye from those prepared from the patient's urine were produced when alloxan was added to urines from normal subjects. It seemed unlikely that T substance and alloxan could be identical due to the well-known instability of alloxan and various differences have been found (for example by ultraviolet absorption spectrography and extractability into n-butanol at pH 5). There is no evidence in this patient, or in any of the other children who have been found to pass comparable quantities of T substance, of any abnormality of carbohydrate metabolism, as might be expected if they were elaborating large amounts of alloxan.

If T substance is derived from purine metabolism it may come from endogenous or exogenous sources. When a virtually purine-free diet consisting of milk and eggs is fed to a patient passing this material it promptly disappears from the urine. Nor does it return when individual

purines and pyrimidines are added to the basic diet in amounts up to 250 mg daily for three to five days. It may be that these are insufficient quantities given for too short a time to allow the reappearance of T substance in the urine for it usually takes several days to return when the patient is put back on a full diet. Uric acid levels in serum and urine are normal or low and fall abruptly during a period on a purine-free regime. Recent work on the chemical nature of T substance suggests that it may be a quinone or quinolone (Wilkinson & Sidle 1960).

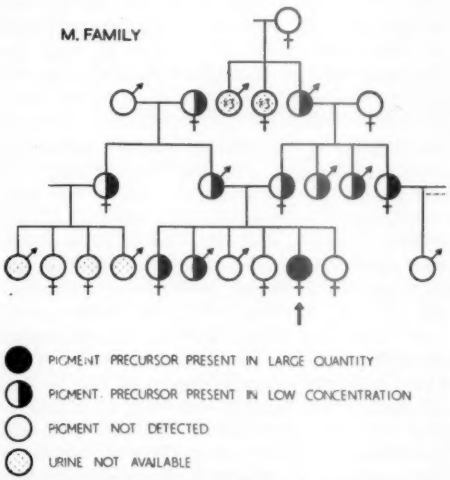
M. FAMILY
PIGMENT PRECURSOR PRESENT IN LARGE QUANTITY
PIGMENT PRECURSOR PRESENT IN LOW CONCENTRATION
PIGMENT NOT DETECTED
URINE NOT AVAILABLE

Fig 2 *Genealogical tree of family M. The arrow indicates N M, the patient*

Mode of inheritance of the metabolic error: 6 children in 4 unrelated families are known to us in whom urinary excretion of T substance occurs in comparably large amounts. They are regarded as being homozygous for the genetic abnormality while individuals passing only small amounts are considered to be heterozygous. Examination of the family trees suggests that the anomaly is transmitted as an autosomal recessive characteristic, e.g. this patient's family (Fig. 2). The parents of all the homozygous children are found to be heterozygous as are many of the ascendants and collaterals. None of these has any disability which can be ascribed to the genetic defect. The observation that females may excrete as large quantities of T substance as males and be equally affected seems to exclude carriage of the abnormal gene on the X-chromosome.

Comment: It does not seem possible to explain any of this child's clinical manifestations by the presence of a horseshoe kidney. Even her continued vomiting does not appear to be related to this abnormality since there is no evidence of urinary tract infection, impaired renal function or hydronephrosis. We think that her failure of mental development is directly associated with the finding of urinary excretion of large quantities of T substance; of the 6 known homozygotes for the metabolic anomaly (the only ones found in the course of chromatography of the urines of nearly 250 children), 3 are grossly mentally retarded (Table 1). We assume that a relationship exists between the homozygotic state and the genesis of the defect in development. The specific nature of the inherited error is not known.

Table 1
Physical and mental status of the six known homozygotes for T substance anomaly

Case 1	T T Gross mental and physical retardation
Case 2	B D Gross physical retardation
Case 3	J D Normal
Case 4	J J Gross mental and physical retardation
Case 5	R J Normal
Case 6*	N M Gross mental retardation

*The case shown.

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Kernicterus in Full-term Infants without Isoimmunization (4 cases)

T Valaes MB DCH, Ph Fessas MD and S A Doxiadis MD

Case 1

First pregnancy of a mother aged 25 who gave no history of previous blood transfusion or injections. Full-term male infant weighing 3,700 g at birth. Delivered in the maternity department of a general hospital in Athens. Jaundice became apparent at the end of forty-eight hours. An I.M.

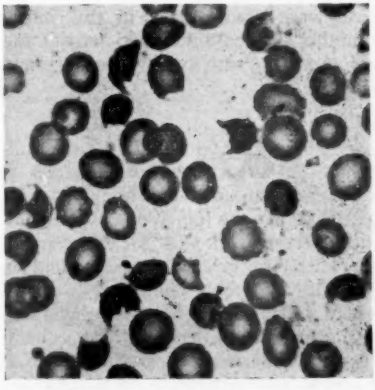

Fig 1 *Fragmented and distorted red cells in Case 1*

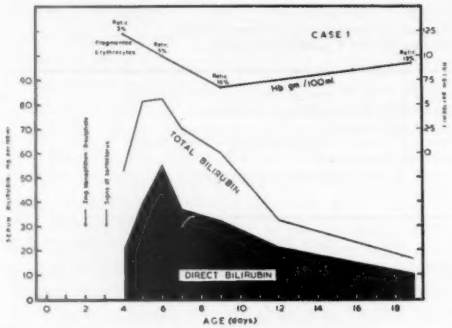

Fig 2 *Course of serum bilirubin aud hæmoglobin in Case 1*

injection of 2 mg of menaphthone bisulphate was given. Jaundice deepened quickly. He stopped sucking the evening of the third day of his life and when admitted to our department he was deeply jaundiced. Spleen was palpable two finger-breadths below the costal margin while the liver was only slightly enlarged. Unmistakable signs of kernicterus were present. Laboratory results: Mother, Group A, Rhesus positive. Infant, Group O, Rhesus positive. Direct Coombs test negative. Hæmoglobin 12·10 g%, hæmatocrit 38%, reticulocytes 3%. A large proportion of the red cells were markedly distorted and fragmented (Fig 1). The course of serum bilirubin and hæmoglobin values is shown in the graph (Fig 2). Jaundice persisted for three weeks, fading gradually. The obstructive element, although prominent biochemically, was obvious clinically only from the bile staining of the urine while fæces were of normal colour. At the age of 10 days liver function tests and plasma protein electrophoresis were normal. At the age of 6 months he was found to be fairly well nourished. He exhibited marked spasticity of all limbs and he was deaf. Complete absence of the enzyme glucose-6-phosphate dehydrogenase was demonstrated in this infant while his mother showed diminished activity and his father normal activity (Motulsky and Campbell test).

Case 2

Mother aged 20, primigravida. Infant male, full-term, normal delivery, birth weight 2,800 g. Jaundice appeared at about 50 hours and increased gradually. On the fourth day, when jaundice was deep, three injections of 2 mg of menaphthone bisulphate were given. When admitted on the fifth day he was deeply jaundiced, liver and spleen were of normal size. There were signs suggesting kernicterus but as these were not conclusive he was treated by an exchange transfusion of 600 ml of compatible fresh blood. By next day the signs of C.N.S. damage were certain. Jaundice

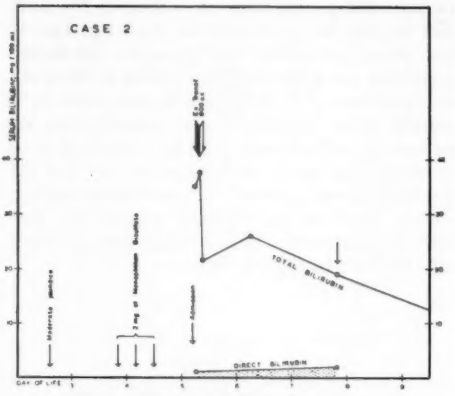

Fig 3 *Course of serum bilirubin in Case 2*

disappeared on the 12th day and the infant was discharged on the 22nd day feeding well. The extent of neurological sequelæ has not yet been fully assessed. Laboratory results: Mother, Group B, Rhesus positive. Infant, Group O, Rhesus positive, direct Coombs test negative. In the pre-exchange blood: Hæmoglobin 15·0 g%, hæmatocrit 46%, reticulocytes 5·5%. No Heinz bodies were seen and there was no morphological abnormality of the red cells. The course of the serum bilirubin values is shown in Fig 3. Red cell survival was studied with ^{51}Cr. In the infant itself and in a normal adult the infant's red cells had a much shortened survival ($T\frac{1}{2}\ ^{51}Cr = 8$ days). The infant had no glucose-6-phosphate dehydrogenase activity in his red cells. Both parents had normal activity.

Case 3

Male infant weighing 3,650 g at birth, delivered at a private nursing home. Mother, primigravida, aged 22. Jaundice appeared at 36 hours of life but during the five-day stay of the infant in the nursing home it did not become deep enough for the attending pædiatrician to ask for any laboratory investigations. On the seventh day of life according to the parents the infant was still jaundiced but active and feeding very well. On this day winter clothes kept with naphthalene moth-balls were taken into the room where the infant was sleeping. Next day jaundice was deeper. When admitted, aged 10 days, he had definite signs of C.N.S. damage, severe jaundice, hepatosplenomegaly and anæmia. The infant died on the 14th day. Post-mortem confirmed the diagnosis of kernicterus. Laboratory results: Mother, Group A, Rhesus positive. Infant, Group O, Rhesus positive. Direct Coombs test negative. Maximum total serum bilirubin 56 mg, Hb 4·6 g%, Heinz bodies in 70% of red cells, many fragmented red cells

(12th day). The infant had diminished glucose-6-phosphate dehydrogenase activity but both parents showed normal activity. A male sibling born recently had normal G-6-PD activity and had no jaundice.

Case 4

Mother, aged 33, gravida III, para I. Infant, female, full-term, normal delivery. Birth weight 2,800 g. She had no apparent congenital abnormalities. Slight jaundice appeared on the fourth day and had increased by the next day. The infant was seen by an experienced pædiatrician who diagnosed 'physiological jaundice'. The baby was not seen again by a doctor till her admission late on the tenth day on account of her lethargy and refusal to feed. On admission the infant was intensely jaundiced and had unmistakable signs of kernicterus. Liver and spleen were of normal size. No history of exposure to known toxic agents could be elicited. She was fully breast-fed, mother and infant received no drugs and neither was exposed to naphthalene. The infant's condition gradually deteriorated and she died with symptoms of kernicterus on the 16th day. Since her admission urinary output seemed normal and there was no hæmoglobinuria. Laboratory results: Mother, Group O, Rhesus positive. Infant, Group A, Rhesus positive. Direct Coombs test negative. Heinz bodies in all red cells, most of them fragmented. Hb 8·5 g%. In all blood-films examined platelets were seen in abundance. The infant and both parents showed normal glucose-6-phosphate dehydrogenase activity of the red cells.

Comment: These cases are representative of many similar cases of severe neonatal jaundice in Greece. About one-third of all exchange transfusions in full-term infants born in the 'Alexandra' State and University Maternity Hospital, Athens, have as only indication a hyperbilirubinæmia without demonstrable incompatibility. The high incidence of this type of severe neonatal jaundice is more striking among the infants who were sent to us with established kernicterus. Among these, 9 out of 10 had no Rhesus or ABO incompatibility.

In about two-thirds of the cases of severe neonatal jaundice without incompatibility we found a deficiency of the glucose-6-phosphate dehydrogenase of their red cells and we postulate that this defect forms the basis of an increased hæmolysis. Extrinsic factors such as naphthalene by inhalation or menaphthone bisulphate by injection were not found in all cases. In the remaining one-third there were infants with similar features but without this enzyme defect.

Chondrodysplasia Epiphysalis Multiplex with Diabetes Mellitus and Mental Retardation

E Tempany MRCPI DCH
(for A P Norman MD FRCP)

N H, female, aged 15.

In November 1949 when admitted to a children's home, she was noted to be extremely under-sized, her hair sparse and coarse and her fingers spatulate. She was mentally retarded. A tentative diagnosis of cretinism was made, and she was treated with thyroid extract.

Since 1953 she has been under the care of a foster mother who says that she can talk but is unable to read. She is of a pleasant disposition

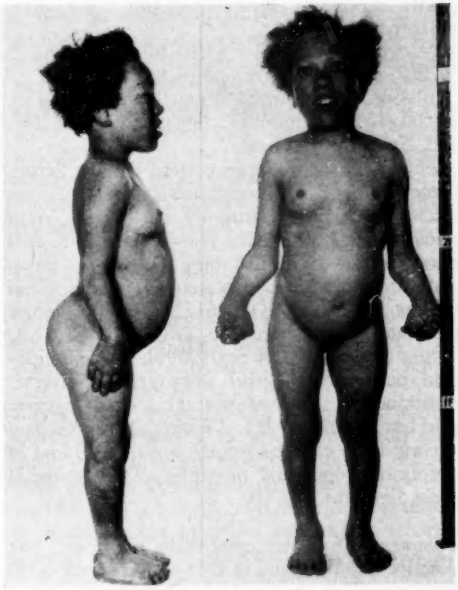

Fig 1

Fig 2

and can carry out simple domestic tasks. In the past seven years she has grown 2 in. Menstruation began in January 1960.

Family history: Father, aged 53, has been a patient in a mental asylum for the past eleven years. Mother has a cleft palate and is retarded. 3 siblings: one aged 17, her brother, has an I.Q. of 102–108. Two others apparently have different fathers.

On examination: Height 39 in. Skull 18½ in. Crown to pubis 22 in. Pubis to heel 17 in. Arm span 37½ in. Weight 43 lb 14 oz. Blood pressure 120/90. Distribution of hair normal though that of the head was coarse in texture. Development of breasts and external genitalia appeared normal for chronological age. Hands large and spatulate. Joints, especially elbow, knee and ankle joints enlarged.

Investigations: Hb 12·8 g/100 ml. P.C.V. 42%. W.B.C. 8,900. Urinalysis normal.

Blood sugar: fasting 165 mg/100 ml. Levels 30, 60, 90, 120, 150 minutes after glucose were 243, 275, 206, 167 mg/100 ml.

Nuclear sex chromatin pattern female. Serum proteins 6·5 g%. Electrophoresis normal. Serum calcium 9·5, phosphorus 4·3 mg/100 ml. Acid phosphatase 4·5, alkaline phosphatase 10·5, acid phosphatase (alcohol-stable) 1·1 K-A units. Total bilirubin 1·0, conjugated 0·4, unconjugated 0·6 mg/100 ml. S.G.O.T. 61, S.G.P.T. 56 moles pyruvate/100 ml serum/h. G.O.T./G.P.T. 1·1. Serum cholesterol 206 mg/100 ml. Urine amino-acid pattern (via resin) shows raised glycine, ornithine and a trace of asparagine. Phenylpyruvic acid test negative. P.B.I. 4·6 µg%. X-ray skeletal survey: bone changes present are those found in dysplasia epiphysalis multiplex. Mental age 4 years 5 months. I.Q. 30.

Comment: Dysplasia epiphysalis multiplex, first described by Fairbank in 1935 and again reported by him in more detail in his book 'Atlas of general affections of the Skeleton' (1951), is characterized by dwarfism, stubby digits and mottling or irregularity in density and outline of the developing epiphyses. The pathology is unknown and probably occurs owing to an enzyme disturbance resulting in interference in the normal development of epiphyseal cartilage.

It appears to be familial and can occur in either sex. Fairbank did not think the condition was familial, but since then there have been a number of reports showing a clear familial incidence, particularly those of Waugh (1952), Barrie *et al.* (1958), and more recently Weinberg *et al.* (1960). The last article reports six generations of a family in which 22 males and 23 females were affected while 32 males and 30 females were normal.

The presenting symptoms are frequently lack of stature or a waddling gait, owing to involvement of the hip-joint. Most cases occur during childhood and, with the exception of those reported by Waugh, no other physical abnormalities have been found. In Waugh's cases the three affected sisters also had cleft palates.

The diagnosis is a radiological one and in the cases reported no biochemical disturbance was found.

The radiological features are seen in the epiphyses. Not all epiphyses are involved, those most frequently affected being the hips, shoulders and ankles. The centres of ossification for these may be late in appearing but the principal change is irregularity in ossification. Epiphyses may arise from more than one centre of ossification, though the main bulk of the epiphysis arises from one centre, unlike dysplasia epiphysalis punctata.

The hips show changes chiefly in the femoral heads, acetabular changes being rare. The femoral head varies in appearance though usually appears more shallow and less convex than normal. Similarly in the shoulder-joints the head of the humerus is affected, being irregular in outline. In the ankle-joint there is obliquity of the talo-tibial joint due to changes chiefly in the lower tibial epiphysis and to lesser extent in the talus. As a result on X-ray the joint line slopes downwards from medial to lateral. The spine is not commonly affected and when changes occur they are chiefly in the dorsal region and affect only the vertebral bodies which appear in A.P. and lateral views to be broader than normal, though their vertical size is not appreciably altered and the disc spaces are normal. The carpus is small in depth and the carpal bones are irregular in shape. The metacarpals and phalanges are short with square heads. The knees show changes involving chiefly the femoral condyles. These appear rectangular in shape with shallowness of the intercondylar notch.

The unusual features of the case reported are the associated lesions of mental retardation and diabetes mellitus. Fairbank (1947) considered the intelligence to be 'usually normal', an observation supported by Weinberg *et al.* (1960), all of whose cases were of normal intelligence. It would appear that the association of these three conditions, namely multiple epiphyseal dysplasia, diabetes mellitus and mental retardation in this patient are coincidental.

Dysplasia epiphysalis multiplex has to be differentiated from other conditions in which epiphyseal changes occur.

In cretinism the patient is dull and apathetic. The P.B.I. and radioactive iodine tests are abnormal and the response to thyroid is seen both clinically and radiologically.

In dysplasia epiphysalis punctata the *whole* of

the epiphysis appears to be ossifying from a number of discrete centres, the shafts of the bones are thick as well as short and the ends may be enlarged and splayed. The tarsal bones may be completely stippled showing nothing but a collection of dots. In addition congenital cataract is frequently found in these cases.

In Morquio-Brailsford disease the changes in the vertebral bodies are a striking feature not seen in dysplasia epiphysalis multiplex. In dyschondroplasia changes tend to be unilateral and mottling is often confined to half the epiphyses and is never seen unless the corresponding portion of the metaphysis contains masses of unossified cartilage. In this condition, the epiphyseal changes are over-shadowed by the metaphyseal changes. In osteopetrosis the shafts of the bones show a marked increase in density.

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Two Children with the Oculo-cerebro-renal Syndrome of Lowe, Terrey and MacLachlan

C E Dent MD FRCP & Jean M Smellie BM MRCP DCH

Case 1 B P, male, born 22.4.41. First attended University College Hospital in October 1954.

History: Second child of healthy, unrelated parents. Normal pregnancy and delivery. Birth weight 5 lb 8 oz. Cataracts noticed at birth. Otherwise considered normal until arrest of progress aged 1 year. Rickets diagnosed and improved with vitamin D therapy (Dr V Smallpeice, Oxford). Active rickets present when he next attended at 4½, and again at 8 years. On each occasion healing followed treatment with vitamin D. Next hospital attendance at 12 years for unsteady gait and increasing knock-knee deformity.
Past history: 7 operations for cataract.
Development: From 1 year slow mentally and physically. Walked at 5–6 years. Odd words with meaning, capable of simple jobs and clean in habits by 10 years.
Family history: Similar elder brother died aged 9 following leg operation.
On examination: Dwarfed (height 41½ in., 50th percentile for four and a half years), mentally retarded, partially sighted boy. Bilateral cataracts. Nystagmus. Marked genu valgum and rachitic rosary. Unco-operative and detached, exhibiting repetitive movements of hands and occasional violent temper.
Investigations (August 1954): Serum calcium 9·4, plasma inorganic phosphorus 2·6 mg/100 ml. Plasma alkaline phosphatase 67·5 K-A units. Plasma HCO_3^- 18 mEq/l. Urine: 0·5 parts/1,000 protein. Electrophoresis: abnormal globulins, 'renal tubular' pattern. Numerous granular casts. Chromatography: moderate low molecular weight amino-aciduria. X-rays: osteoporosis and active rickets.
Treatment and progress: Alkalis produced no rise in plasma HCO_3^- and no mental or radiological improvement. Vitamin D (calciferol, dihydrotachysterol and vitamin D_2) has produced healing of rickets, lowering of plasma alkaline phosphatase, a rise in serum calcium and correction of acidosis. Amino-aciduria has decreased and was completely absent when he was briefly intoxicated with vitamin D. Growth of 12½ in. in six years. Present height 54½ in. (50th percentile for nine years). Since his admission in 1957 to St. Lawrence's Hospital, Caterham, he has become more obedient and has learnt several new skills. Pubertal changes occurred about 16. Epiphyses not yet united.

Case 2 R H, male, born 23.9.49.
History: First child of healthy, unrelated parents. Normal pregnancy and delivery. Birth weight 6 lb 12 oz. Cataracts noticed at three days. Three operations at Moorfields Hospital. Now able to recognize people and enjoy television.
Development: Normal until 12 months. Joining words at 3. Walking alone 4½ years, delay attributed to visual defect. Odd jobs around the house from 6 years. Dry during day from 8 years. Not walking well for one to two months, now refuses to walk. Recent injury to right knee – X-rays showed rickets. Transferred from care of Dr A Barlow, Ashford Hospital, for further study.
Family history: Brother aged 3½ years similarly affected. Normal sister. Parents apparently normal.
On examination: Dwarfed, mentally retarded child. (Height 44 in., 50th percentile for five and a half years.) Enlargement and tenderness of metaphyses. Mild genu valgum and rachitic rosary. Detached, repetitive movements of hands. Nystagmus – treated cataracts.
Investigations: Serum calcium 9·3, plasma phosphorus 2·1, blood urea 26 mg/100 ml. Plasma alkaline phosphatase 80 K-A units. Plasma HCO_3^- 20·6 mEq/l. Urine: proteinuria 1·0 parts/1,000. Electrophoresis: abnormal globulins, 'renal tubular' pattern. Numerous granular casts. Chromatography: moderate low molecular weight amino-aciduria. X-rays: osteoporosis and active rickets (Fig 1).

Discussion: We consider that these two boys fit exactly into the new syndrome described by Lowe *et al.* (1952) under the name 'Organic aciduria, decreased renal ammonia production, hydrophthalmos and mental retardation'. There have been several further cases described since (Denys *et al.* 1958, Schoen & Young 1959), and the name 'oculo-cerebro-renal syndrome' is now usually preferred. Although many bizarre features are included in the syndrome – cataracts, hyporeflexia, rickets, amino-aciduria and behaviour peculiarities – it is remarkable how homogeneous the disease has appeared to be. Previous cases described in infants do not, however, uniformly include the presence of radiological rickets. We presume it will always develop later. Our Case 2 is of interest in that rickets was not diagnosed until his admission to hospital at the age of 11 years. The cause of the rickets is presumably related to the gross disorder of renal tubular function which resembles in many ways that occurring in cystinosis. It is of interest that we were able to heal the rickets in Case 1 over a six-year period, with vitamin D alone. Except for a short trial period we did not give alkalis as recommended by the original authors, who stressed the acidosis present and the need for its correction.

Fig 1 *Case 2, R H, aged 11 years: X-ray of right knee. There are florid rachitic changes of recent origin in the metaphyses with no signs of hyperparathyroid erosions. The bone cortex is thin indicating a marked degree of osteoporosis. There are lines of arrested growth in the shafts and especially near the rachitic metaphyses indicating probably previous lesser metabolic disturbances*

Each of our cases has a brother identically affected, the families otherwise being clinically normal. Clearly we have here a further example of a syndrome in which severe mental deficiency, among other disorders, is closely related to abnormal metabolism of genetic origin – a true inborn error of metabolism in which, however, the site of the primary enzymic deficiency remains to be discovered. We presume that the disease is more common than previously considered.

A more detailed description of Case 1 is in course of preparation (Bound *et al.* 1961).

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Dr George N Donnell: In 1958 the recognition of a typical case at Los Angeles Childrens Hospital aroused great interest in this syndrome. Search of the hospital records uncovered 4 additional cases indexed under the category of cataracts, glaucoma and proteinuria. 10 more were found in the course of investigating the families of these children.

The cause of the oculo-cerebral-renal syndrome is not known. Previous workers have suggested a genetic origin, based primarily on the finding that the disease was limited to males. Until recently, however, data from families were insufficient to construct an acceptable hypothesis for the mode of transmission of the defect. The findings in our 5 families, together with the single family reported by Lefebvre *et al.* (1957), indicate a sex-linked form of inheritance. The condition affects only males, and male siblings have an equal chance of being unaffected. The pedigrees indicate that it is transmitted by the female carrier. Father-to-son transmission has not been encountered.

Initially failure to recognize clinical manifestations in females suggested a recessive gene. This opinion had to be revised, however, because of our observations made during search for a means of detecting the asymptomatic carrier. It was possible to examine the parents, a number of siblings and relatives of affected children. Lenticular cataracts were present in three of the mothers and in one maternal grandmother. In the latter case senile cataracts could not be excluded. In addition in 4 other mothers slit-lamp examination revealed numerous punctate opacities throughout the cortex of both crystalline lenses. Similar lenticular changes were present in 2 maternal grandmothers, 1 maternal great aunt and 3 female children. Only 1 male out of 9 examined, the father of an affected child, had similar findings but to a lesser degree.

Similar anomalies of the crystalline lens are seen

sporadically in normal people during slit-lamp examinations, but the association in this instance is sufficiently striking to suggest expression in the heterozygote.

Complete expression in the female is possible as a result of mating of an affected male with a heterozygote female. This would seem most unlikely in view of the severity of the manifestations in males.

No other evidence of the carrier state was found. Urine from parents and siblings failed to disclose abnormal amino-acids or proteins.

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The following cases were also shown:

Epilepsy with Hyperventilation
Dr J Lorber

Idiopathic Hyperlipæmia
Dr K S Holt

Vascular Ring and Congenital Lobar Emphysema
Dr I M Anderson

Papillœdema During Withdrawal of Steroid Therapy
Dr P F Benson (for Dr R C Mac Keith)

Chronic Regional Ileitis (Crohn's Disease)
Dr S M Tucker (for Dr J N O'Reilly)

Dermatomyositis
Dr P G Wallis (for Dr R H Dobbs)

Infantile Spasms with Hypsarrhythmia
Dr P G Wallis (for Dr A D M Jackson)

Meeting November 25 1960

A discussion was held on **Infantile Hip Disease** and the following papers were read:

Ætiological Factors in Congenital Dislocation of the Hip and Their Bearing on Treatment
Dr C Carter & Mr J A Wilkinson

A fuller account of this paper will be found in *J. Bone Jt. Surg.* 1960, **42**, 669.

The Pathogenesis of Paralytic Dislocation of the Hip in Infants and Neonates
Mr W J W Sharrard

Ætiological Mechanisms of Dislocation of the Hips in Infants
Mr E W Somerville

Meeting December 16 1960

President's Address

The Course of Still's Disease and Results of Steroid Therapy[1] [*Summary*]

by B E Schlesinger OBE FRCP (*London*)

Despite extensive study the pathogenesis of Still's disease remains obscure. It is now usually included in a composite group of collagen disorders as there is some common ground in the histology, but there are many discrepancies. An affinity between rheumatic and rheumatoid disease has often been mentioned, but rheumatoid disease seems to be unrelated to a preceding streptococcal infection, which is now the accepted ætiological factor in acute rheumatism. Moreover the incidence of juvenile rheumatism has fallen in England, whereas Still's disease remains at about the same level.

[1]For a full account of this Address *see* Schlesinger *et al.* (1961) *Arch. Dis. Childh.* **36**, 65

Clinical Course

The age of onset is considerably earlier than that of rheumatic fever and the disease can often begin in infancy.

Still's disease may be confined to many systems of the body before the joints are affected, so that at first the true diagnosis is often obscured. Then the average interval between systemic and arthritic involvement is four months, but it may be considerably longer. Fever may be very high and the child extremely ill. Under these circumstances steroid therapy is particularly effective. Occasionally pyrexia assumes a peculiar periodicity, but with greater irregularity than in Hodgkin's disease and brucellosis.

A rash occurs in about 40% of patients and, rarely, it may be almost the sole manifestation. Purpuric striæ and even gangrenous lesions have been seen.

Leucocytosis, predominantly polymorphonuclear, is a well-known phenomenon of the florid

stage and may lead to an erroneous diagnosis of osteomyelitis or suppurative arthritis when a single joint is at first involved. Occasionally the picture is reversed and profound pancytopenia develops.

There is some evidence that trauma may be a precipitating cause of the disease. Lymphadenopathy is more a sign of systemic than arthritic involvement.

In addition to the characteristic polyarthritis of Still's disease there are other types, such as fleeting arthralgia, affection of the cervical spine with associated torticollis, monarticular involvement, intermittent hydrarthrosis and crico-arytenoid inflammation, causing stridor and respiratory embarrassment.

Among the complications, pericarditis can be acute and obvious, or insidious. It does not necessarily have the same serious implication as in acute rheumatism, since myocarditis is less evident and endocarditis is absent. Iridocyclitis carries a bad prognosis for sight; and amyloid degeneration, though rare, is by no means fatal. Nodules can appear over the usual bony points, but rarely they may arise in muscle, where they degenerate and become necrotic. Nodules have also been found in the skull, producing irregular areas of destruction, which heal in a remarkable manner on steroid therapy.

Dermatomyositis is sometimes closely associated with rheumatoid disease in the same child.

Treatment

Steroid therapy should be used in all but the mildest cases. It is far superior to aspirin, which in our experience is not effective. There is no advantage in combining the two treatments. Prednisolone is recommended, and it is now becoming increasingly apparent that if ACTH gel injections are used in conjunction with this the total dose of steroids can eventually be reduced to an amount which is less likely to produce side-effects and which will yet remain effective. At first the dose of steroids should be high and then gradually reduced to a maintenance level just short of producing fresh symptoms.

The best results are obtained when treatment is begun during the first six months of the disease, but it is also effective if started later. A prolonged course must be anticipated, the average duration required being eighteen months, but some children have to continue treatment for some years. More than one course is necessary when there is a recurrence of the disease after steroids have been stopped. After five years' remission relapses are unusual.

The immediate effect of this treatment is dramatic both on the systemic and arthritic manifestations of the disease. The long-term results are also gratifying, since by modifying joint stiffness and swelling it is possible to prevent serious and permanent damage in the majority of children. Intra-articular hydrocortisone injections can also be helpful when there are large effusions.

The most serious side-effect is osteoporosis, which may proceed to marked wedging and even collapse of the vertebræ. This is not irreversible, and if a periodic radiological check is kept on the spine, the dose of steroids can then be reduced and the vertebræ will eventually recalcify normally. Attempts to prevent this by supplementary oral calcium and a high protein diet should always be made but will not always be successful. Anabolic steroid therapy has proved disappointing, as have other cortisone analogues, such as triamcinolone. We prescribe potassium chloride and oral penicillin to neutralize possible electrolyte disturbances and prevent masked infection.

Should an infection develop or surgery be required, the dose of steroids should be temporarily raised, otherwise a disastrous reaction may occur.

Other forms of drug therapy have been tried, such as phenylbutazone, chloroquine and gold, but in our hands they have proved too toxic.

Clinical experience has therefore convinced us of the value of steroid therapy when serious systemic disease or severe joint disturbance persists after conservative measures have failed.

These investigations comprise a hundred cases followed for up to fifteen years, with the help of my colleagues, Dr C C Forsyth, Dr R H R White, Dr J M Smellie and Dr C E Stroud at the Hospital for Sick Children, Great Ormond Street, and University College Hospital.

I cannot end this Address better than by paying homage to the man who first described this disease in children – Sir George Frederic Still. Though small in stature, he was great in mind. I was his House Physician and so I can vouch for this with some conviction. He was the first doctor in this country to devote his entire medical life to diseases of childhood. He was the father of British pædiatrics. We who follow owe him a tremendous debt, and the story I have told is meant as a small though, I fear, quite inadequate tribute to him.

Section of Endocrinology

President H L Sheehan MD

Meeting November 23 1960

Cases

Invasive Pituitary Tumour, with Cushing's Disease, Treated with Pituitary Implantation of Gold-198 Seeds

G F Joplin MRCP and Russell Fraser FRCP

D J, aged 27, male nurse with drug-resistant open cavitating pulmonary tuberculosis.

History: First seen at Hammersmith Hospital 6.7.60, with (1) increasing obesity, with striae, œdema and weakness – eighteen months, (2) Right III nerve palsy, increasing in severity – thirteen months.

Cushing's syndrome first clinically suspected May 1959, but 17-K.S. and K.G.S. normal. May 1960: suspected right parasellar space-occupying lesion (National Hospital, Queen Square), based on slight upward displacement of carotid siphon. Cushing's syndrome proven June 1960 (Dr R I S Bayliss), and patient referred for consideration of pituitary implantation with radio-active seeds.

Pre-implant assessment: Obviously cushingoid. Partial right III and IV nerve pareses. Normal visual fields. Blood pressure 130/90. Pituitary fossa area in lateral skull film 66 sq. mm (normal <130 sq. mm, Joplin & Fraser 1960), with slight irregularity of floor. Air encephalogram: No upward extension from pituitary fossa. Pre-sacral oxygen insufflation: right adrenal hyperplastic (left not demonstrated). C.S.F.: protein 62 mg%. No cells. 17-K.S.: 26 mg/24 h; 17-K.G.S. 25 mg/24 h. Dexamethasone (4 mg/day), caused suppression only to 5 mg and 5 mg respectively on seventh day (normal K.G.S. fall to <1 mg/24 h, normal data to be published). Glucose tolerance test normal. Prednisone glycosuria test (Joplin *et al.* 1961): overnight glycosuria 122 mg/h ($n<60$) i.e. pre-diabetic tendency.

Treatment: Transethmoid needle implantation (15.7.60) of 7 seeds of gold-198 (1·8 mc each). 77% of the gland was calculated to have received $>10{,}000$ rads, while peak dose to diaphragma sellæ $=6{,}000$ rads. Dose to right III nerve $=1{,}000$ rads.

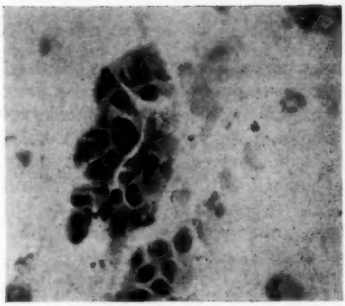

Fig 1 *Pituitary biopsy. H & E* ×370

Pituitary biopsy (Fig 1): 'Crooke cells seen. Nuclear irregularity . . . might be invasive.'

Progress: Rapid onset of peeling and decrease of cushingoid features. 17-K.G.S. fell to 13 mg on ninth and tenth days. No hormone replacement therapy has been required at any stage.

Reassessment at four months: Features no longer cushingoid. Striæ pale. Generally fitter. III nerve regenerated with loss of ptosis. 17-K.S. and K.G.S.: 9 and 7 mg/24 h. Only suppressed by dexamethasone to 5 mg and 5 mg /24 h. Prednisone glycosuria test: 23 mg/h. Forty-eight hour neck uptake of $^{131}I = 32\%$ (normal).

Comment: The presence of an invasive pituitary tumour was suggested by the oculomotor pareses occurring in the absence of a radiologically enlarged pituitary fossa (Jefferson 1955), and later the biopsy obtained during the implant procedure was also found consistent. The simultaneous onset of Cushing's syndrome implies that it was secreting ACTH. The failure of dexamethasone to cause complete suppression of adrenal steroid output in the normal way suggests the abnormal level of adrenal function; although a very satisfactory clinical remission followed interstitial irradiation, the continuing lack of suppressibility by dexamethasone suggests the persistence of

independent activity of the pituitary, although at a lower level. The III nerve palsy, probably due to tumour invasion, was also improved by the implant.

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Acromegaly Hyperparathyroidism and Diabetes Mellitus

A J Bowdler MRCP and
Arnold Bloom MD MRCP

Miss E W, aged 48, a box maker.

History: At the age of 21 her face enlarged following three attacks of erysipelas, and she grew 4 inches in eight months. When aged 35, enlargement of the hands and fingers. From the age of 39, suffered from a flexural eczema and recurrent cellulitis and blepharitis. Admitted to Whittington Hospital in diabetic ketosis at the age of 46. No members of her family have been known to show any endocrine abnormality.

On examination (May 1958): Prominent facial features and mild spade-like appearance of the hands. Marked pitting œdema of the feet. Extensive furunculosis; chronic blepharitis. No neuropathy or retinopathy. Blood pressure 150/90. Visual fields normal.

Investigations: Skull X-ray showed an enlarged pituitary fossa and a large mandible (Fig 1), and X-ray of the hands suggested increased tufting of the terminal phalanges. Blood cholesterol 112 and 142 mg%. B.M.R. +14%.

Fig 1 *Lateral skull X-ray. Note enlargement of pituitary fossa*

Subsequent course: The diabetes was controlled with a low carbohydrate diet and insulin, the daily requirement varying between 20 and 120 units. Recurrent superficial infections occurred and an electrophoretic strip showed a slightly raised gamma-globulin. White cell counts were normal.

October 1958: Plasma inorganic phosphorus 3·6 mg%.

January 1959: Paræsthesiæ in both hands.

June 1959: Successfully treated by surgery for carpal tunnel syndrome. Hb 14·8 g%, W.B.C. 6,000, urinary 17-hydroxycorticosteroids 10·4 mg/24 h, serum calcium 11·2 and inorganic phosphorus 1·9 mg%.

November 1959: Serum calcium 13, inorganic phosphorus 2 mg%, urinary calcium (on ward diet) 790 mg/24 h, plasma alkaline phosphatase 7 K-A. units, blood urea 36 mg%, serum cholesterol 206 mg%, and 17-hydroxycorticosteroids 13 mg/24 h. ^{131}I studies of thyroid function within normal limits (neck-thigh ratio 3·8; two-hour thyroid uptake 12·1%). No abnormality was seen in a barium swallow and meal. Fractional test meal showed achlorhydria.

The patient was transferred with a diagnosis of hyperparathyroidism complicating acromegaly and diabetes to the care of Professor C E Dent at University College Hospital, where studies of the calcium and phosphorus balance (shown in Fig 2) were performed. Before operation, the plasma calcium was high, the plasma phosphorus low, and there was a very slight negative calcium balance of about 78 mg per day. The very high urinary loss of calcium (about 750 mg daily) was nearly balanced by the high level of calcium absorption from the gut, only 590 mg of calcium appearing in the fæces per day while the patient was taking 1,250 mg in the diet. Tests were also made for the 'reciprocation effect' by reducing the phosphorus absorbed from the gut with colloidal aluminium hydroxide, and by increasing it with a supplement of neutral sodium phosphate. Reciprocation is demonstrated when a change in the plasma inorganic phosphate is followed by a converse change in the plasma calcium. This was well seen both pre- and post-operatively when phosphate absorption was increased, but was less marked with the aluminium hydroxide.

Other investigations showed normal plasma electrolytes, plasma urea 39 mg%, urine specific gravity 1002 to 1020, and urinary 17-ketosteroids 5·8 mg/24 h and 17-ketogenic steroids 9·0 mg/24 h. Plasma calcium fractions were: ionized 6·8, complexed 0·5, protein-bound 4·1 mg%. X-rays of the abbreviated skeleton confirmed the enlargement of the pituitary fossa, but the bones were generally well calcified and there were no bony changes of hyperparathyroidism.

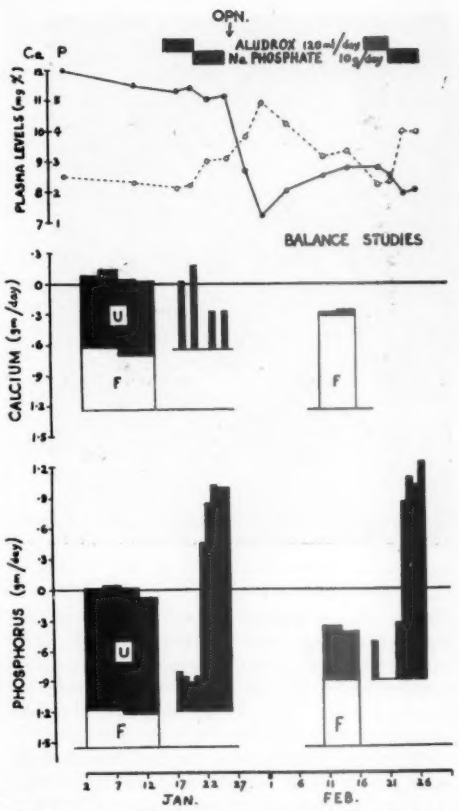

Fig 2 *Graphs of plasma calcium and phosphorus levels, calcium balance and phosphorus balance. Plasma calcium* ●—●, *plasma inorganic phosphate* ○---○. *In balance charts, intake plotted downwards from the zero line, and shown as the horizontal baseline on which the fæcal and urinary outputs are built up. Negative balance indicated by the sum of the outputs rising above the zero line. 'F', fæcal output. 'U', urinary output*

Exploration of neck 27.1.60 (Mr D R Davies): Two enlarged parathyroids were found on the left side, the upper being lobulated. Two normal parathyroids were identified on the right, and biopsied. The histology of frozen sections appeared normal. The two enlarged glands were removed, and microscopically these showed mainly an excess of chief cells arranged in an acinar pattern and in cords, with prominent islands of oxyphil cells (Fig 3). No rim of normal tissue was identified at the periphery of the gland, and the appearances were consistent with either chief-cell hyperplasia or adenoma.

Following operation the plasma calcium fell to 7 mg%, and rose to normal six weeks later. On testing two weeks after operation, the calcium balance was positive, and the renal phosphate threshold had risen from the pre-operative level of 1·9 mg% to 3·0 mg%. The reciprocation effect was still demonstrable.

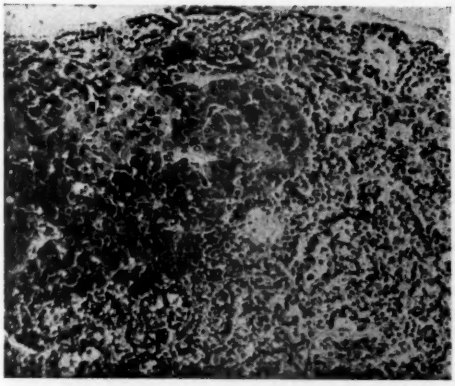

Fig 3 *Section from enlarged parathyroid. Note the acinar arrangement of chief-cells about an island composed mainly of oxyphil cells.* (*H & E* × 130.)

Discussion: The post-operative plasma values, the calcium balance, and the rise in the renal threshold for phosphate show that removal of the two enlarged parathyroids corrected the hyperparathyroidism in this patient, and that these were, therefore, responsible for the hyperparathyroid state.

Cases such as this have been described under the titles of 'polyglandular syndrome' or 'the syndrome of multiple endocrine adenomas' showing enlargement or overactivity of more than one endocrine gland. These were reviewed by Underdahl *et al.* (1953): the commonly involved glands are the anterior pituitary, the parathyroids and the islet tissue of the pancreas; and often, though not invariably, enlargement of a gland has been accompanied by overactivity. Some cases have features closely resembling those of the Zollinger-Ellison syndrome, a remarkable example being described by Zubrod (1958).

The familial tendency to this condition was confirmed by Wermer (1954) and a genetic basis was therefore suggested for the condition, presumably mediated by an autosomal dominant gene. However, as in the present case, evidence of a familial tendency may be completely lacking, and it may well be that the syndrome can arise from an acquired tendency to proliferation of glandular tissues, the origin of which may lie in the pituitary (Harrison & Fraser 1960). Relevant to this is the suggestion that the underlying process is one of hyperplasia rather than of adenoma formation *per se* (Keynes 1960). With regard to the parathyroids, Cope *et al.* (1958)

suggest that these are most commonly affected in this syndrome by a condition which they describe as 'primary chief-cell hyperplasia', in which all the cell types are involved in a proliferative process. By histology alone, the individual gland may be indistinguishable from an adenoma, although in some cases the adenoma has a rim of normal tissue peripherally.

The cases so far described with chief-cell hyperplasia have shown all four parathyroids to be involved, and it is not known at present whether it may affect the glands asynchronously. If this were possible, then cases such as the present one might later show a relapse of the hyperparathyroidism as the hyperplasia affected the remaining glands. It is thus of considerable importance that such cases should have prolonged supervision with this in mind, as well as there being the possibility of other manifestations of the syndrome arising.

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Lymphadenoid Goitre with Hypothyroidism, Exophthalmos, Pretibial Myxœdema and Acropachy

Mary C Peard MB DCH
(for Raymond Greene DM FRCP)

Mrs J W, aged 28, was first seen in July 1951, complaining of staring eyes, swollen neck, and increased growth of hair on the front of her legs, all present since the birth of her first child in the previous February. There were no other symptoms of thyroid disorder.

Between 1942 and 1944 she gained weight from 177 to 219 lb, and reduced to 168 lb by dieting and taking small doses of thyroid. After parturition in February 1951, she again dieted and took thyroid gr $\frac{3}{4}$ daily, reducing her weight from 183 to 169 lb. She was taking thyroid gr $\frac{3}{4}$ at the onset of her symptoms. Menstrual history was normal. Her paternal aunt suffered from thyrotoxicosis.

On examination: Tall and heavily built with large, rather masculine hands and feet. She had a stare, due largely to upper lid retraction, the exophthalmometer readings being at the upper limit of normal, i.e. 1·7 cm (Fig 1). Upper and lower lids puffy; no chemosis. Fingers and toes slightly clubbed: slight pretibial myxœdema with hairiness of the skin (Fig 2). She had a small hard goitre with the consistency typical of Hashimoto's

Fig 1

disease. There were no other signs of thyroid disorder; and no other abnormal physical signs.

A diagnosis of Hashimoto's disease with unusual features was made, but as she was already under treatment with thyroid, no investigations were instituted. Thyroid was increased to gr 3 daily.

During the next few months, the exophthalmos increased to 2 cm, and the pretibial myxœdema

Fig 2

and clubbing became worse. Thyroid treatment was discontinued and after a suitable interval, she was admitted for investigation: B.M.R. −24%. Serum cholesterol 325 mg%. Radioiodine test: T=1·2 (normal 3 to 13). Plasma proteins: abnormally high α_2 and γ globulin. 17-ketosteroids (Callow) 8·5 mg, 17-hydroxycorticoids (Norymberski) 12·3 mg. ECG typical of hypothyroidism. Biopsy of skin: characteristic of myxœdema. Biopsy of thyroid: much fibrosis, Hürthle cell degeneration, almost complete absence of colloid in a lymphadenoid goitre. X-rays of hands and feet showed irregular periosteal new bone formation along ulnar borders of shafts of first metacarpals suggestive of early pulmonary osteoarthropathy.

Despite an increase in thyroid dosage to gr 5 daily, the pretibial myxœdema, clubbing and exophthalmos continued to deteriorate. Her general condition improved and the thyroid gland gradually diminished and ultimately became impalpable. By 1953 her condition was unchanged except for the pretibial myxœdema which gradually became worse. At various times in the next few years, the following treatments (for the pretibial myxœdema) were given unsuccessfully: X-rays, short wave diathermy, local and intra-arterial injections of hyaluronidase, local injections of triiodothyronine (T3) and hydrocortisone, inunction of T3 and hydrocortisone, cortisone acetate by mouth, Martin's bandages and large doses of various thyroid 'analogues'. In 1954 hypothyroidism reappeared. Since then it has been necessary to raise the dose to between gr 12 and gr 15 of thyroid, or its equivalent. Her present euthyroid state is maintained with 15 tabs. (25 µg) T3 daily, i.e. 375 µg. In 1956 various thyroid analogues were administered in high dosage with the object of producing hyperthyroidism. None of these appeared clinically to affect her metabolism except for T3, which produced a slight tachycardia, although Triac temporarily produced a normal B.M.R. and serum cholesterol (see Table 1). Further experiments with oral doses of labelled ^{131}I thyroxine and triiodothyronine have indicated normal absorption, storage, excretion and half-life.

Comment: In 1933 Thomas described a negro male with exophthalmos and a toxic goitre. Within eight months of partial thyroidectomy he developed some clubbing of the fingers. Three years later he became hypothyroid, and had marked clubbing of the fingers, with subperiosteal new bone formation in the phalanges. Since 1933 several cases have been described, most of them with thyrotoxicosis initially, but others with no evidence of thyrotoxicosis at any stage. For example there has been no evidence of thyrotoxicosis in this patient, and in a previous case described by Raymond Greene (1951) there was doubt about the existence of previous hyperthyroidism.

Table 1
Effect of thyroid analogues on B.M.R. and serum cholesterol

Date	*Treatment*	*Daily dose (mg)*	*B.M.R. (%)*	*Cholesterol (mg%)*
20. 6.56	T3	0·1	−22	350
13. 7.56	Triac	3	−22	300–400
24. 7.56	Triac	7	−15	139–185
20. 8.56	Triac	10	−3 to +2	183–210
23.10.56	Triac	12	−6 to 0	200–235
3. 6.57	Diiodothyronine	4	−25	215–285
27. 6.57	Diiodothyronine	7	−21	250
23. 7.57	Diiodothyronine	14	−25	233

The development of hypothyroidism is the feature common to these cases in which the triad of exophthalmos, pretibial myxœdema and clubbing is described. While exophthalmos is usually present early in the illness, its rapid progression, and the appearance of clubbing and pretibial myxœdema may occur at any time. In 1937 Cushing described the appearance of clubbing, seven years after partial thyroidectomy for toxic goitre with exopthalmos.

The patient now described is unusual since she presents this curious triad of signs in association with hypothyroidism due to Hashimoto's disease. Furthermore, the hypothyroidism is extremely resistant to any form of thyroid therapy.

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Chronic Thyrotoxic Myopathy

C W H Havard DM MRCP
(for A W Spence MD FRCP)

Mr G C, aged 62.

History: October 1959: Onset of diplopia on looking upwards. Slight loss of weight despite good appetite. April 1960: Noticed that eyes were becoming more prominent. Progressive weakness of both legs, and to a lesser extent both arms. By October could only walk 500 yards without having to stop. Had pain and difficulty in moving eyes. Loss of 2 st. in weight over previous eighteen months.

Past history: 1920: Infective hepatitis. 1945: Onset of dysphagia. Achalasia of the cardia diagnosed, since when he has been passing a bougie every morning. 1959: Admitted to hospital with œdema of legs. Subacute nephritis diagnosed. Œdema and albuminuria resolved on bed rest alone.

Fig 1 *G C, 3.11.60*

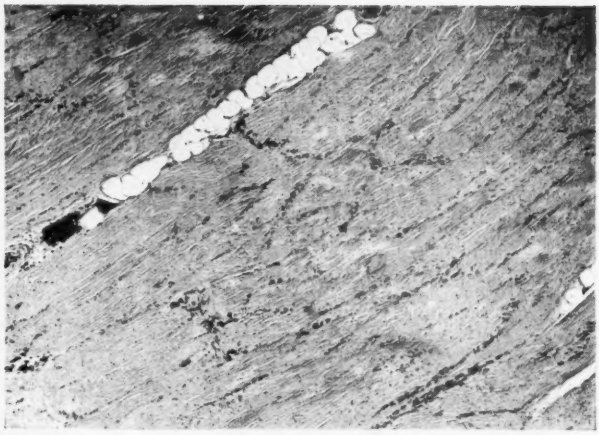

Fig 2 *Quadriceps muscle biopsy. H & E×60*

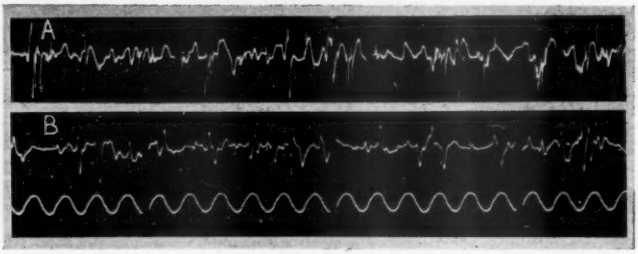

Fig 3 A, *patient—from quadriceps.* B, *normal—from quadriceps*

Physical examination: Slight bilateral exophthalmos, more marked on right. Bilateral lid retraction, more marked on left. Conjunctival congestion with hypertrophic caruncles. Limitation of upward movement of right eye associated with diplopia. Pupils normal. Enlarged right lobe of thyroid gland with bruit. Limbs warm and moist. Fine tremor of outstretched hands. No pretibial myxœdema. Many lipomata over arms and legs. Pulse regular, rate 90. Blood pressure 160/70. C.N.S.: Marked muscle weakness and wasting of limbs, especially of the buttock, thigh and shoulder girdle muscles (Fig 1). Just able to raise his thighs off the bed. Reflexes present and equal. No sensory change. Plantar responses flexor.

Investigations: E.S.R. 7 mm in 1 h (Westergren). Blood count normal. Urine: no albumin or sugar. Centrifuged deposit normal.

Tests of thyroid function: Plasma protein-bound iodine: 11 µg/100 ml. Radioactive iodine uptake: 69% uptake at two hours; 88% at six hours. Ratio of activity in the blood at two hours and forty-eight hours was 6:1, which indicates hyperthyroid function.

Chemistry: Fasting blood sugar 91 mg%. Plasma albumin 4·7, globulin 1·6 g%. Electrophoresis normal. Blood urea 37 mg%.

Investigations of myopathy: Prostigmin test negative. No urinary creatine. Biopsy of quadriceps muscle showed atrophy of voluntary muscle fibres with considerable concentration of sarcolemmal nuclei; some adipose replacement of muscle fibres (Fig 2). Electromyography (Dr E D M Campbell): Right and left deltoid – no fibrillation; on volition many normal units were obtained, though patches throughout the muscle consisted of disintegrated motor unit potentials. Left quadriceps: Many more disintegrated motor unit potentials in this muscle (Fig 3).

X-rays: Chest: Lungs clear. No evidence of any anterior mediastinal tumour. Thoracic inlet normal. Skull: Normal. Barium swallow: Barium passed down the œsophagus into the stomach without any delay when standing. Minimal delay at cardia when recumbent. Peristalsis in œsophagus was good and there was no significant dilatation of the œsophagus.

Treatment: 8 mc of ^{131}I, were given on October 19, 1960.

Discussion: The association of thyrotoxicosis and muscle weakness has long been recognized. Both

Graves in 1835 and Basedow in 1840 drew attention to this symptom. In its milder form it is common enough and is frequently, though probably incorrectly, attributed to the general asthenia. There are, however, patients with thyrotoxicosis in whom the muscular weakness and wasting may be entirely out of proportion to the degree of thyrotoxicosis, and some 40 cases of this so-called chronic thyrotoxic myopathy have been reported.

Our patient shows many of the features typical of his type of myopathy (Fig 1). The muscle wasting here, as almost universally, affects the proximal muscle groups particularly the lower limbs. There are, however, records of 3 untreated patients in whom the paresis spread to involve the muscles of respiration and they died from respiratory paralysis (Morgan & Williams 1940, McEachern & Ross 1942, Thorn & Eder, 1946). It is now realized that treatment of the hyperthyroidism is uniformly successful in restoring the muscle function to normality.

In addition to thyrotoxic myopathy our patient had exophthalmic ophthalmoplegia; this association is uncommon; eye signs are usually absent, and indeed, apart from weight loss, which is striking, the symptoms and signs of thyrotoxicosis are frequently masked.

Creatinuria is a frequent feature in thyrotoxic myopathy, though there is no correlation between the extent of the creatinuria and the degree of paresis. There was no creatinuria in our patient. Similarly Zierler (1951) found an absence of creatinuria in his patients: he also noted, however, that they had an impaired creatine tolerance, a combination of events which he attributed to defective hepatic synthesis of creatine.

The electromyographic changes found in our patient were typical of myopathy (Fig 3). Normal volitional activity of voluntary muscle is made by the asynchronous contraction of individual motor units: each unit consists of the bundles of muscle fibres supplied by one anterior horn cell and its motor neuron. Electrically the activity of the fibres of the unit summate smoothly to give a monophasic, diphasic or triphasic wave, which varies between 4 and 10 msec in duration. In neuropathies whole units supplied by the diseased nerves will perish but the dominant frequency of the wave form will be unchanged. In primary disease of muscle, however, individual muscle fibres die sporadically: as some of the components of the units are missing the activity of the fibres ceases to summate smoothly, and many polyphasic potentials are seen; these are of shorter duration and usually of the order of 1 msec.

Electromyographic signs of myopathy occur in patients with only slight musuclar weakness (Hed *et al.* 1958). This, in association with the defective creatine metabolism frequent in patients with typical hyperthyroidism, suggests that the muscular weakness in thyrotoxicosis is often a true myopathy and not just part of the general asthenia.

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Iodide Goitre

A Dimitriadou MD[1] and Russell Fraser FRCP

Miss P P, aged 24

History: April 1959: Painless neck swelling, general health good. For three months she had taken 1½–2 oz per day of a proprietary blood mixture (including 0·4–0·5 mg iodine per day), for a skin complaint. No family or previous history of goitre.

On examination: A nervous, plump, euthyroid woman. Pulse 110, regular; hands warm with mild coarse tremor, slight puffiness of upper eyelids; thyroid firm, diffusely enlarged, about 160 g, no bruit.

Investigations: (*a*) Before stopping the blood mixture (6.5.59): Hb 10·4 g%, W.B.C. 2,800. E.S.R. 8 mm in 1 h (Westergren). Serum cholesterol 364 mg%. Plasma thyroid antibodies weakly positive, viz. thyroglobulin tanned red cell agglutination test positive 1/2500 (precipitin test negative), complement-fixation test positive 1/160.

(*b*) One month after stopping the blood mixture (9.6.59): B.M.R. +10%. Plasma P.B.^{127}I 4·6 µg%. Serum cholesterol 206 mg%. ECG normal. ^{131}I test: neck uptake at forty-eight hours 62%, urinary excretion at forty-eight hours 19%. P.B.^{131}I at forty-eight hours 0·95%/l. A thyroid biopsy at forty-eight hours showed a histology of a non-toxic goitre, and biochemical findings noted below. A repeat ^{131}I test after six days on triiodothyronine 120 µg/day gave a urinary excretion at forty-eight hours of 74% (i.e. normal suppression).

Course: Six weeks after stopping the blood mixture the thyroid was soft and only 40 g. Potassium iodide, 30 mg/day, given intermittently for four months, made the thyroid firm and larger – about 100 g. Stopping potassium iodide reduced the thyroid again to 40 g. Four months subsequently, the ^{131}I uptake was normal; U_{48}=50%, N_{48}=49%, P.B.$^{131}I_{48}$=0·08%/l.; and was little altered on its repeating with 2 mg potassium iodide carrier added (Feinberg *et al.* 1959) viz. U_{48}=52%, N_{48}=36%; unlike the iodide goitres reported by Paris *et al.* (1960).

The results of digesting the thyroid biopsy at forty-eight hours after the second ^{131}I dose (9.6.59) gave the findings summarized in Table 1, i.e. a low total iodine content, an abnormally small proportion of ^{131}I reaching the monoiodotyrosine (MIT) or later stages of iodination, and also an abnormally small proportion of ^{127}I as iodothyronine or diiodotyrosine (DIT), and an undue proportion as iodide.

Discussion: This case is clearly a typical iodide goitre as indicated in the history, though it is of interest that one year later there is still a small goitre. The rarity

[1] Supported by a grant from the Wellcome Trust.

Table I
Chromatographic analysis of biopsy digest

	Unknown	*Iodide*	*MIT*	*DIT*	*I-thyronines*	*Total*
^{131}I	24	27 (17)	12·5 (13)	12·5 (43)	24 (22)	62%of dose (42)
^{127}I		46 (18)	45 (28)	9 (30)	1 (24)	1·4 mg (10)

Values expressed as percentages of the total iodine content. Normal figures in brackets (unpublished data).

of this syndrome despite the large number of persons receiving iodide in medications for various diseases, suggests that these goitres only develop in abnormal glands. The biopsy indicated two defects. Even when free of the excess iodide the gland was still inefficient in synthesizing thyronines, particularly in binding the iodide at the first steps to MIT. Possibly this was the basic defect in her gland which made her susceptible to an iodide goitre. At this stage also it showed iodide depletion coupled with an avidity for ^{131}I, comparable with that seen after the withdrawal of prolonged dosage of any antithyroid drug.

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Longstanding Diabetes Mellitus without Complications, and Graves' Disease followed by Spontaneous Myxoedema

J Smith MB and I C Gilliland MD

Miss Y C, aged 72.

History: 1913: Palpitations, bulging of the eyes, loss of weight and nervousness. Graves' disease was diagnosed; two years' rest was prescribed and resulted in spontaneous remission including eye signs. 1919: Again started to lose weight, developed boils and suffered from pruritus vulvæ. Diabetes mellitus was diagnosed and she was put on to a strict diet consisting of eggs, cheese, meat, fish and 1 oz bread daily for five days in the week; for the other two days, she was allowed only beef tea. She continued on this regime until two years after the advent of insulin. She was then started on insulin, of which her initial dose was 5 units daily; the dose has subsequently been gradually increased. Throughout the whole course of her diabetes, she has weighed all her food, tested her urine four times a day, and attended her doctor and diabetic clinic regularly. In 1959, she complained of baggy eyes, increased sensitivity to cold, general mental slowing and severe constipation. She presented the classical appearance of myxœdema which was confirmed by the usual tests. Serum cholesterol 530 mg%; ECG showed low voltage and flattening of T waves; ^{131}I test showed a neck uptake of 20% at forty-eight hours, and a 'T' value of 1·7 (Fraser *et al.* 1953). She was treated with sod. I-thyroxine, and the response was excellent. Her ECG became normal, and her cholesterol 210 mg%. A glucose tolerance test was done twenty-four hours after the last insulin dose, in May 1959, and the results were as follows: Fasting 260, 30 min 350, 60 min 490, 90 min 520 mg%. At present she is being maintained on 20 units a day of Insulin Lente, and is on a daily allowance of 140 g carbohydrate.

Family history: No known diabetes mellitus or thyroid disorder.

On examination (November 1960): Slight ptosis of right eye. The pupils were equal and reacted well to light and accommodation. An early cataract was evident in the right eye. Several small microaneurysms were seen in both fundi, but no other retinal change (Fig 1). Blood pressure 130/80, peripheral pulses all present, reflexes all present and equal. No parasthesiæ, no albuminuria.

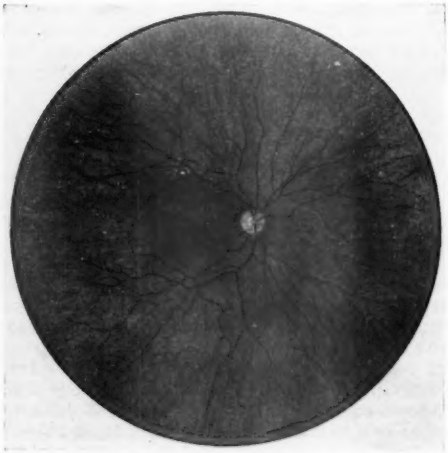

Fig 1

Comment: The case was shown, as an example of insulin-requiring diabetes mellitus for forty-one years, with very slight complications. She was also remarkable in that she had had Graves' disease in youth, with spontaneous myxœdema supervening forty-seven years later. This patient has always taken the most exceptional care with her diet and insulin, and has sought advice regularly. She would be classed in Group 1 of the series described by Joslin & Wilson (1950).

It seems likely that a study of those patients who avoid the major complications might be as rewarding as the more usual study of those who are afflicted.

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Book reviews

Man's Posture
Electromyographic Studies
by J Joseph MD MRCOG
American Lecture Series No 386
pp x+88 illustrated 44s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

Numerous investigations into the mechanism of muscle tone and the part this plays in the maintenance of posture have produced conflicting results. In this monograph Dr Joseph energetically sets out to clarify the situation. He confines himself mainly to the investigation in man of one posture, that of standing at ease. By the use of surface electrodes and an amplifier with an extremely low noise level he was able to detect the smallest degree of motor unit activity within the main muscles of the lower limbs and spine.

He demonstrates that resting muscle shows no electrical activity which can be ascribed to motor unit activity and suggests the term 'muscle tone' should be reserved to refer to its ability to respond to stretch. In the standing at ease position only the calf muscles show motor unit activity. From this he concludes that the stability of the ankle-joint is maintained by the calf muscles, but at the hip and knee joints by the appropriate ligaments.

The book is well produced with adequate illustrations and contains an exhaustive review of the subject with a full list of references.

Controlled Clinical Trials
Papers delivered at the Conference convened by the Council for International Organizations of Medical Sciences
organized under the direction of
Professor A Bradford Hill FRS
pp vii+177 illustrated 20s
Oxford: Blackwell Scientific Publications Ltd 1960

This slender volume is a gem, indeed more – a precious jewel. It consists of a series of short papers delivered at a conference convened in Vienna in 1959 by the Council for International Organizations of Medical Sciences, established under the joint auspices of UNESCO and WHO. The papers were all given by Englishmen. Bradford Hill was the captain of the all-star team which included so many of those who have made British clinical trials the envy of the scientific world and the despair, sometimes, of the pharmaceutical industry. In almost equal proportion were statisticians – Armitage, Doll, Knowelden, Reid and Sutherland – and the clinicians – Atkins, Bywaters, Kellgren, Paterson, Pickering, Scadding and Witts. And then there were those who are at home almost anywhere on the field – Crofton, Cruickshank, D'Arcy Hart and Fletcher.

Originally there was no intention to publish these papers because already there is an extensive literature, but public demand has called for it and the result is a most readable and interesting account of how to conduct a clinical trial, and how to determine whether a new drug is more effective than another. At a time when pharmaceutical firms are daily producing new compounds and their advertising divisions are bombarding the doctor with promotional literature, it is essential that the profession should be educated in how to assess the claims made, and that doctors working in hospitals should know how to set up valid clinical trials. This book should be read by every member of the medical profession – young or old. Students too should be familiar with it; how much more profitably those umpteen hours spent on learning forensic medicine could be devoted to this topic.

The Clinical Apprentice: A Handbook of Bedside Methods
by John M Naish MD FRCP
and John Apley MD FRCP
2nd ed pp vi+199 illustrated 12s 6d
Bristol: John Wright & Sons Ltd 1960

This is an inexpensive little book which slips easily into the pocket. It is designed as an introduction to clinical medicine and as such it contains much useful advice. The text is readable, the index is worth while. There are a number of good illustrations but some of the numerous diagrams have little point.

Attenuated Infection
The Germ Theory in Contemporary Perspective
by Harold J Simon MD PhD
pp xvi+349 illustrated 80s
London: Pitman Medical Publishing Co Ltd
Philadelphia & Montreal: J B Lippincott Company 1960

The author of this book believes that the germ theory of disease needs refurbishing because, in its original form, it did not sufficiently recognize that, though the infectious microbes are necessary for infective disease, they are not sufficient: the host and the environment also have a fundamentally important part to play. Moreover the

original theory regarded overt illness as the common consequence of infection. It now is clear that inapparent infections are far more common than apparent. It is to these inapparent infections that the author applies the term 'attenuated', and in this essay he surveys the nature and frequency of attenuated infection in man, animals, plants, insects and tissue cultures; he reviews the factors that promote attenuation and those that lead attenuated infections to become manifest. There are also chapters on the mutual relations of attenuated infection in man and in animals with emphasis on its potential clinical importance. The whole is treated on the broadest of canvases.

The basic idea behind the book represents a fascinating problem, and the numerous examples given make most interesting reading. But the breadth of the canvas has taken charge and the argument is repeatedly lost in the pursuit of entertaining, but only distantly relevant, by-ways, so that by the 300th page one certainly needs the author's 'Epitome' to remind one of what the book was intending to say. The message would have been clearer in fewer pages, but there is much to stimulate and many suggestions of avenues for future exploration.

Good English for Medical Writers
by Ffrangcon Roberts MA MD FFR
pp ix+176 17s 6d
London: William Heinemann Medical Books Ltd 1960

Dr Ffrangcon Roberts' little book is timely, as any reader of medical or scientific journals in English and its American variants will agree.

No one of us, however carefully we strive, can write impeccable English. We have our foibles, our pet circumlocutions, some of us a passion for coining or for using neologisms and most of us a reluctance to write and rewrite until we have said what we have to say in the fewest and the clearest terms.

Unfortunately, many do not even try to write clearly, and some do not even know how to do it. For both classes, this book should be compulsory reading. It covers much the same ground as does Sir Ernest Gowers' 'Complete Plain Words', but perhaps is not quite so reliable a guide to usage, though with the advantage of a knowledge of medical terminology that enables the author to see that Gowers' proposed expression 'lameness from time to time' is not an adequate substitute for 'intermittent claudication', and that amongst ourselves we must use our technical language, even if it be not understood by the laity.

To write on English is, as the author admits, a dangerous task, and amongst the clumsy or ungrammatical sentences he cites and corrects, there are a few in which his changes are not changes for the better. He gives two variants of a passage which discusses the liability to error of psychiatrists (p 77). His own is clearly the worse version of the two, and what the passage has to say can be said in fewer and clearer terms: viz. 'Psychiatrists are not more immune from self-deception than are our Great Planners or our Medical Politicians'. At the bottom of page 165 is a proposed sentence that would read more simply and briefly as follows: 'Too often, stored tablets become stale and inert; they should be fresh.'

He dislikes 'dysarthria' and proposes 'dysphonia' as a substitute, but the two terms refer to different disorders. There are some good maxims in the book: 'If you want to learn to write well you must write, rewrite and rewrite again'. He adds, feelingly, 'I suffer, just as much as others do, the agonies of composition'. Agonies indeed they are, but how well worth enduring when clarity and conciseness emerge from them.

Chromatographic and Electrophoretic Techniques
by Ivor Smith BSC PHD FRIC
2nd ed Vol I Chromatography pp xvii+617 illustrated 65s Vol II Zone Electrophoresis pp viii+215 illustrated 30s
London: William Heinemann Medical Books Ltd 1960

The twin techniques of chromatography and paper electrophoresis have revolutionized the work of biochemists in clinical and other laboratories, and although there is a spate of journals, review publications and books covering the field, the expansion within two years of the first edition of this invaluable volume into two is to be welcomed; nowhere else is so much information so conveniently gathered together. Almost every conceivable practical application of the two techniques has been described in detail and appropriately illustrated. Volume I of this new edition includes new or revised sections on the chromatography of purines, pyrimidines, organic acids, cholesterol and radioactive substances; the use of ion exchange cellulose is also described. Volume II is a mine of information on paper electrophoresis and also describes the more recently developed methods using starch, cellulose acetate, agar gel and foam rubber as supporting media; there is a particularly valuable account of the use of high voltages and of immuno-electrophoresis. In both volumes an attempt has been made for all the methods described to be based upon standard but simple and easily acquired apparatus. These two volumes will be invaluable for all hospital biochemists and chemical pathologists, especially on account of the numerous reviews of clinical application. They are so exceptionally well produced and comprehensive that they are worth the rather high price.

Congenital Deformities
by Gavin C Gordon MB FRCSE
pp vii+127 illustrated 37s 6d
Edinburgh & London: E & S Livingstone Ltd 1961

This book is concerned with one congenital deformity alone, dislocation of the hip. Its argument and method of exposition can be best shown by direct quotation: 'In the antenatal position of fully flexed hips and crossed legs, displacement occurs on extension, with a strong tendency to reposition when the fœtal position is resumed. This results in a recurrent dynamic process. No fixed displacement occurs unless severe pressure effects supervene. Postnatally the action of the legs alters, so that the emphasis is on extension, the fœtal position of crossed legs in flexion becoming a memory. In these circumstances the displacement would tend to be progressive and fixed, not recurrent, and with the onset of ossification in the first year, dysplasia will become apparent. In other words, the biomechanics of the joint progress and change inevitably in ontogenetic growth, and if the morphological effects as exemplified by the stability of the joint are insufficient at vital stages, then fixed dislocation develops in post-natal life'.

There are a number of X-rays, with explanations of them which would certainly not be generally accepted; e.g. Figs 24, 25 and 26, in which radiographs most surgeons would pass as normal are demonstrated as showing that recurrent dislocation occurred before birth on the evidence of 'multiple skin folds on the affected side'. The short book ends with sections on osteomyelitis, osteoarthritis and cerebral palsy, which are brought into the argument as being what the author calls 'phenocopies' and defines as conditions 'similar to the one caused by genetic influences but not present in the genetic constitution'.

It is a strange book.

Cancer of the Rectum
edited by Cuthbert E Dukes OBE MD MSC FRCS
Vol III of Monographs on Neoplastic Disease at Various Sites
general editor: D W Smithers MD FRCP FFR
pp xiii+303 illustrated 50s
Edinburgh & London: E & S Livingstone Ltd 1960

This book is one of a series of monographs planned to deal with neoplasms at individual sites which, when completed, should prove of immense value to all of us who are concerned with malignant disease.

The present volume has 18 expert contributors and deals in a compact manner with every facet of rectal malignancy, even including tumours of the large bowel in mammals other than man. Successive sections deal with statistics, predisposing factors, pathology, clinical, anatomical and physiological features, treatment and post-operative care. Finally there is a detailed analysis of the results of surgical treatment of rectal cancer at St Mark's Hospital and an appendix on vital statistics as applied particularly to rectal growths.

As an example of the authoritative approach to the subject, the choice of operation is expertly debated by Goligher; and separate detailed accounts then follow on abdomino-perineal excision by Abel, perineo-abdominal excision by Gabriel, the synchronous combined operation by Lloyd-Davies and conservative resection by Naunton Morgan. Their descriptions are so good that at first the reviewer did not notice the absence of illustrations in these sections!

References are copious and include 1959. The book is beautifully produced and represents an altogether praiseworthy contribution to this important subject.

Chemical Osteosynthesis in Orthopædic Surgery
by Michael P Mandarino MD
pp x+72 illustrated 36s
American Lecture Series No 391
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

This monograph deals with experimental and clinical experiences with Ostamer, a polyurethane foam. The first chapter is concerned with the chemistry of the polyurethanes, but fails to disclose the precise chemical composition of Ostamer beyond pointing out that its basic constituents are a resin containing two or more hydroxyl groups per molecule, a di-isocyanate, water and a catalyst.

The animal experiments to investigate the tissue response to Ostamer were divided into three sections namely 'toxicologic, metabolic pathways, and orthopædic'. The possible toxic effects were examined histologically, hæmatologically and by tissue culture, but no permanent adverse reactions were noted. One year after implantation in rats, 60% of the implanted Ostamer had been excreted, 20% remained at the site of implantation, and 20% was found in the subcutaneous fatty tissue. The results of the 'orthopædic' experiments were considered to be excellent. The photomicrographs in this section are poor and add little to the information contained in the text.

Indications for the use of Ostamer in human orthopædic surgery, together with a description and pictures of the 'Mandarino' operation, are given. In some cases intramedullary rods are recommended in addition to the plastic for greater strength.

Finally, 50 patients operated upon by the author are reviewed but in the assessment of these

only 36 are listed, of whom '28 healed uneventfully, 5 continued to drain and 3 were failures'.

The information in this book is inadequate for proper evaluation of the material described.

Recent Advances in Pathology
edited by C V Harrison MD
7th ed pp xi+459 illustrated 48s
London: J & A Churchill Ltd 1960

This latest edition of Recent Advances in Pathology is the work of several contributors, and has been edited by Professor C V Harrison who has himself contributed sections on diseases of lymphoid tissue, arteries, and liver. Not surprisingly with several contributors, differences in style may be observed from chapter to chapter, but these do not greatly detract from the readability and clarity of the work.

The guiding principle aimed at by the editor has been the selection of subjects in which there have recently been advances likely to be permanent, and in which the latest information is not readily available in standard textbooks. This aim has been most successfully achieved.

Because of careful selection of subject matter the practising morbid anatomist will find not only a survey of recent advances but a great deal of information on these topics that cause difficulty in routine work.

This edition is well produced and clearly printed; it can be whole-heartedly recommended.

The Practitioners' Handbook
edited by W A R Thomson MD
pp xxiv+711 63s
London: Cassell 1960

This book contains nearly three hundred very short articles which were originally published in 'Revision Corner' in the *Practitioner*. The authors, all consultants, are nearly as numerous as the articles. The subjects are scattered widely over the field of medicine, but with a slight preponderance in obstetrics, gynæcology and pædiatrics. Each subject was originally chosen because it presented the general practitioner with a frequent difficulty, for example 'The child who won't eat', 'Backache in women', 'The clinical significance of vertigo'. The aim is to provide on these subjects an authoritative, concise and practical review of those methods of diagnosis and treatment which have proved acceptable and reliable. It is not a comprehensive textbook.

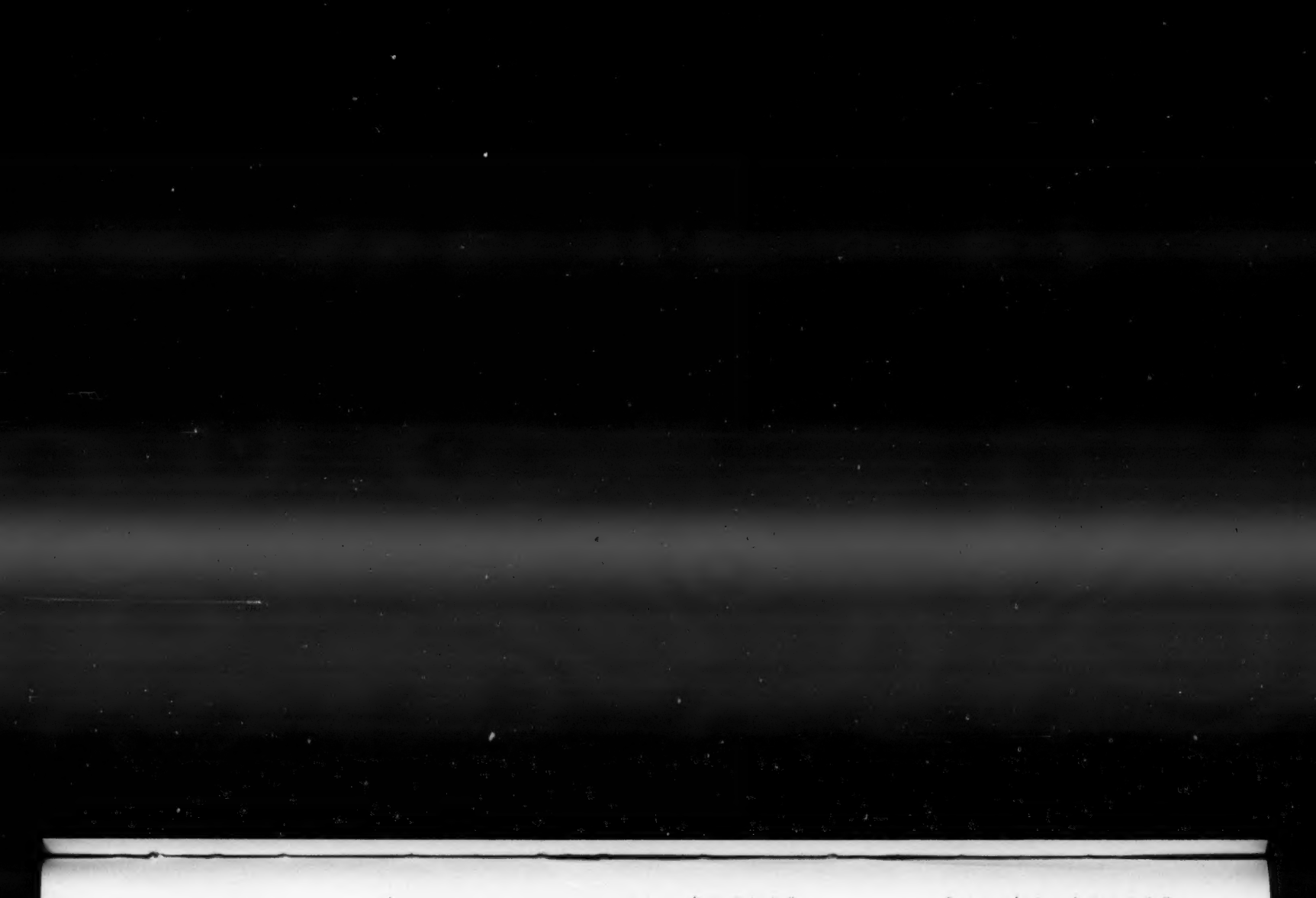
It is an excellent book with the immense merit that every article is short. The choice of subjects is appropriate; a few would be difficult to find in standard textbooks – for instance, halitosis, proctalgia, freckles, menstrual hygiene – but the majority represent common problems in practice; major problems such as 'The treatment of myocardial infarction' appear alongside minor ones.

The book could be useful to the young doctor with problems that he has not met before and to the older physician who wants to be sure that he is up to date. Where so many difficult subjects are discussed, no reader could fail to find much that is new to him.

Essentials of Human Embryology
by Frank D Allan MS PHD
pp xiii+225 illustrated 40s
New York: Oxford University Press 1960

The author describes this book as a synopsis of human embryology for the medical student. The chapters are arranged in condensed form and no attempt is made to discuss the more controversial aspects of embryology, and only the most basic considerations are given to histogenesis as it is assumed that this will be found in books on morphological anatomy. The book is subdivided into conventional subsections, and in these the development of the different tissues and organ systems are dogmatically stated. A final chapter dealing with abnormal development does little more than enumerate the more common abnormalities found without attempting to discuss how these might have arisen. The role of immunological factors as a cause of abnormalities is dismissed in four lines.

The illustrations are, as the author states, of 'heterogenous origin' and as they are only line drawings without colour, many of them do little more than present schemes of the developing embryo. This book will only be of value to the student who requires a very superficial knowledge of the subject.

Embolic Dispersoids in Health and Disease
by Gus Schreiber BS MD
American Lecture Series No 390
pp xvi+85 illustrated 44s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

The word 'dispersoid' is used to describe microscopic particles of starch, cellulose, silicate, lipid and the like which the author finds present in preparations of human blood. Since the width of these dispersoids is often 20–60 microns, they must often act as emboli and produce microscopic infarcts in the tissues. Such infarcts may be the cause of disease and often of ageing itself. The book describes the author's methods and presents summaries of the frequency with which dispersoids are revealed by such methods. It does no more than hint at the pathological implications of the findings, which are to be discussed elsewhere.